NHS England

Evidence review: Proton beam therapy for breast cancer

NHS England

Evidence review: Proton beam therapy for breast cancer

First published: October 2019

Updated: Not applicable

Prepared by: Solutions for Public Health (SPH) on behalf of NHS England Specialised Commissioning

Contents

1 Introduction

Introduction

- Breast cancer is the most common cancer in the UK accounting for 15% of all new cancer cases in 2016 (CRUK 2019a).
- The most common symptoms of breast cancer include a breast lump, a change in the appearance or feel of a breast, pain, changes to the texture of the skin or the position of the nipple or fluid leakage from the nipple (CRUK 2019b).
- Treatment options include surgery to remove the tumour, radiotherapy, chemotherapy, targeted therapies and hormone therapy (NHS Choices 2016).

Existing guidance from the National Institute of Health and Care Excellence (NICE)

- NICE have not published any guidance on the use of proton beam therapy in breast cancer.

The indication and epidemiology

- In 2016 there were 54,500 new cases of female invasive breast cancer and 360 new cases of male breast cancer in the UK (CRUK 2019a).
- Annual incidence rates for breast cancer in the UK are projected to rise by 2% between 2014 and 2035 to 210 cases per 100,000 females (CRUK 2019a).
- About one in seven women in the UK will be diagnosed with breast cancer at some point in their lifetime. Almost half of breast cancer cases diagnosed in the UK each year are in people aged 65 and over (CRUK 2019a).
- The prognosis for breast cancer has improved in recent decades in the UK with a five year survival of 87% and a ten year survival of 78% (CRUK 2019a).

Standard treatment and pathway of care

- Photon radiotherapy is standard care in the NHS in England.

The intervention (and licensed indication)

- Proton beam therapy (PBT) is an alternative to conventional photon radiotherapy.
- Photons deliver a continuous energy beam which can cause damage to surrounding healthy tissue (CADTH 2017). Protons deliver most of their energy deposition at a near-fixed point or target (the Bragg peak), after which essentially no dose is deposited (Verma et al 2016). Protons deposit minimal energy before and after the tumour, thereby sparing healthy tissue (CADTH 2017).

Rationale for use

- The improvement in long-term survival amongst breast cancer patients has increased concerns about the longer-term side effects of radiotherapy for breast cancer (NHS England unpublished communication).
- There is therefore interest in methods of delivering radiotherapy more precisely to the tissues that need irradiating whilst minimising radiotherapy dose to nearby normal tissue.

2 Summary of results

- Fourteen studies were included in this evidence review. These were three retrospective comparisons of PBT and photon radiotherapy, ten case series on PBT and one cost effectiveness study. No controlled studies comparing the clinical effectiveness or safety of PBT and photon radiotherapy were identified.
- One of the three retrospective comparisons included 724,492 patients consisting of 871 PBT patients and 723,621 photon radiotherapy patients (Chowdhary et al 2019). The other two retrospective comparisons had 86 (39 PBT and 47 photon radiotherapy) and 129 (72 PBT and 57 photon radiotherapy) patients respectively (DeCesaris et al 2019, Teichman et al 2018). Sample sizes in the ten case series ranged from ten to 100. Six of these were prospective case series (Luo et al 2019, Smith et al 2019, Bradley et al 2016, Bush et al 2014, Chang et al 2013, MacDonald et al 2013). Four were retrospective case series (Liang et al 2018, Ovalle et al 2018, Verma et al 2017, Cuaron et al 2015).

Clinical effectiveness[1]

- **Overall survival/ mortality** (one retrospective comparison (n=724,492) and four case series (total n= 263 (range 30 to 100)): In the retrospective comparison five year overall survival was 91.9% for PBT patients (n=871) and 88.9% for photon radiotherapy patients (n=723,621). PBT was not associated with overall survival in multivariate analysis (hazard ratio 0.85 (95%CI 0.68 to 1.07), p=0.168). In three case series overall survival ranged from 95% to 100% for median follow-up ranging from 35 months to five years. One case series reported mortality at 7% with a median follow-up of 15.5 months.
- **Disease progression[2]** (five case series, total n=293 (range 30 to 100)): Disease free survival[3] was 94% at a median follow-up of five years in one case series and disease failure[4] was 13% at a median follow-up of 15.5 months in another case series. Loco-regional disease free survival was 96% and 97% (95%CI 93% to 100%) in two case series with median follow-up of 35 months and five years respectively. In another case series there were no cases of loco-regional recurrence at a median follow-up of 59 months. Metastasis free survival was 84% at a median follow-up of 35 months in one case series. In two other case series 3% and 0% of patients developed distant metastasis with median follow-up of 9.3 months and 59 months respectively.
- **Physician-rated cosmetic outcome[5]** (two case series, total n=130 (range 30 to 100)): In one case series the proportion of physicians reporting an '*excellent*' or '*good*' cosmetic outcome was approximately 95%[6] from baseline to a median follow-up of five years. In the second case series the proportion of outcomes rated '*excellent*' or '*good*' was 84% at the end of radiotherapy (n=30) and 69% at three years follow-up (n=23). In this study mean percentage breast retraction increased significantly over time from 10.5% at the end of treatment to 15.3% at three years (p=0.002).

[1] 95% confidence intervals and standard deviations are provided where reported
[2] A range of outcomes relating to local, regional or distant disease progression were reported in the case series
[3] Not further defined
[4] Including loco-regional recurrence and distant disease
[5] One study used an author-developed scale and one study the Harvard Cosmesis Scale. In both cases outcomes were rated as '*excellent*', '*good*', '*fair*' or '*poor*'. One study also reported percentage of breast retraction assessed by comparing the lateral and vertical displacement of the nipple in the treated breast compared to the untreated breast
[6] These data were presented graphically in the study and precise figures were not reported

- **Patient-reported cosmetic outcome[7]/ body image[8]** (one retrospective comparison (n=129) and one case series (n=100)): In the retrospective comparison mean (standard deviation (SD)) cosmetic outcome was statistically significantly better for PBT patients (n=69) vs photon radiotherapy patients (n=56) (3.40 (0.75) vs 2.44 (0.96), p<0.001) at a median of 6.5 years post-diagnosis. Body image was also statistically significantly better for PBT patients (n=72) vs photon radiotherapy patients (n=57) (12.04 (3.75) vs 13.91 (5.25), p<0.03). In the case series, the proportion of PBT patients reporting an '*excellent*' or '*good*' cosmetic outcome was between approximately 90% and 95%[6] from baseline to a median follow-up of five years.
- **Patient-reported treatment outcome[9]/ general perspective[10]** (one retrospective comparison) (n=129)): For treatment outcomes at a median of 6.5 years post-diagnosis, PBT (n=72) was statistically significantly better than photon radiotherapy (n=57) for the mean cosmetic subdomain (1.45 vs 1.88, p<0.001). However the mean pain subdomain was statistically significantly worse with PBT (1.42 vs 1.25, p<0.005) and there was no significant difference in the functionality (1.11 vs 1.17, p=0.311) or oedema (1.07 vs 1.12, p=0.526) subdomains. For general perspective, mean scores were statistically significantly better for PBT patients for five (of nine) questions: '*happy with treatment choice*' (4.92 vs 4.20, p<0.001), '*skin "felt different" since treatment*' (1.22 vs 1.95, p<0.001), '*changed attitude about sex*' (1.41 vs 1.94, p=0.012), '*breast cancer changed views of "myself and body*"' (1.57 vs 2.16, p=0.008) and '*worry about "disease coming back*"' (2.31 vs 3.27, p<0.001). However, mean score was statistically significantly worse with PBT for one question: '*skin quality during treatment*' (1.50 vs 2.82, p<0.001). There was no significant difference for three questions: '*changed how I live my daily life*' (2.00 vs 2.30, p=0.197), '*role of spirituality/ religion*' (4.35 vs 4.00, p=0.116) and '*upper arms/ mobility issues*' (1.19 vs 1.30, p=0.348).
- **Quality of life[11]** (one case series (n=30)): There were no significant differences in quality of life before treatment and after the last day of PBT for any of the 21 subscales assessed on a general or breast cancer specific quality of life questionnaire.

Safety

- **Adverse events** (two retrospective comparisons (n=86 and n=129) and ten case series (total n=432 (range 10 to 100)): Some studies reported a range of adverse events. Others reported specific safety outcomes such as skin toxicity, fatigue or complications for PBT patients who had received immediate reconstruction following mastectomy.
- No Grade 5 (death) or Grade 4 (life threatening) adverse events were reported.

[7] Assessed by the Harvard Cosmesis Scale which rates cosmetic result as 4 ='*excellent*', 3 ='*good*', 2 ='*fair*' or 1 ='*poor*'

[8] Assessed by the Body Image Scale. A 10-item self-reported questionnaire assessing feelings about appearance and changes which may have resulted from a disease or treatment during the prior week. Scored from 1 to 4 with higher scores indicating more dissatisfaction/ negative feelings, where 1 ='*not at all*', 2 ='*a little*', 3 ='*quite a bit*', 4 ='*very much*'

[9] Assessed by the Breast Cancer Treatment Outcome Scale. A 22-item questionnaire evaluating functional and cosmetic outcome, reported as 4 subdomains: cosmetic, breast specific pain, functionality and oedema. Items are scored from 1 to 4 based on any difference between the treated and untreated breast where 1 = '*none*', 2 = '*slight*', 3 = '*moderate*' and 4 = '*large (major)*'

[10] Assessed by 9 questions generated by the study authors which were scored on a 5-point scale from 1 = '*not at all*' to 5 = '*very much*'

[11] Assessed by the European Organization for Research and Treatment of Cancer 30 Quality of Life Questionnaire (EORTC QLQ-C30) and the EORTC breast cancer specific questionnaire (EORTC QLQ-BR23). These are scored out of 100 with higher functional scores and lower symptoms scores indicating better quality of life. The EORTC QLQ-C30 includes 6 functional subscales (global health status, physical, role, emotional cognitive and social functioning) and 9 symptom subscales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties). The EORTC QLQ-BR23 includes 3 functional subscales (body image, sexual function and future perspective) and 3 symptom subscales (systemic therapy side effects, breast symptoms and arm symptoms)

- In one retrospective comparison, there was no significant difference in Grade 3 (severe) acute[12] radiation dermatitis between PBT (n=39) and photon radiotherapy (n=47) (5.1% vs 4.3%, p=0.848). Grade 3 adverse events reported in seven case series included radiation dermatitis (between two and ten cases in four studies) and single cases of pneumonitis, breast/ chest wall pain, wet desquamation and fatigue.
- In one retrospective comparison, acute radiation dermatitis ≥ Grade 2 (moderate) was statistically significantly higher with PBT vs photon radiotherapy (69.2% vs 29.8%, p<0.001). There was no significant difference in ≥ Grade 2 acute skin hyperpigmentation (7.7% vs 12.8%, p=0.502). Grade 2 adverse events reported in nine case series included radiation dermatitis (between 33% and 100% in six studies); oesophagitis (between 2% and 33% in four studies); pain (between 24% and 29% in three studies); fatigue (between 2% and 42% in four studies); skin hyperpigmentation (between 30% and 75% in two studies); erythema/ moist/ wet desquamation (between 7% and 100% in three studies); induration (7% in one study); infection (10% in one study) and oedema (3% in one study). In addition, one study reported 5% of patients with skin hyperpigmentation that was described as moderate/ severe and two cases of moderate or severe retraction or significant asymmetry between breasts.
- In one retrospective comparison mean (SD) fatigue[13] was statistically significantly better for PBT patients (n=72) vs photon radiotherapy patients (n=57) (15.3 (17.11) vs 27.25 (22.26), p<0.002) at a median of 6.5 years post-diagnosis. The proportion of patients responding '*yes*' to the question '*have you felt unusually tired or fatigued in the last week*' was 25% for PBT (n=71) and 63% (n=51) for photon radiotherapy. No significance test was reported.
- Reconstruction complications, reported in two case series, were experienced by 27% and 39% of patients respectively. These patients received PBT after a mastectomy with immediate reconstruction. In one study five of 26 patients (19%) had implants removed. In the other study eight of 51 patients (16%) had implants removed.
- Other ungraded adverse events reported included small numbers of cases of skin infection, rib fracture and clinically evident lymphoedema.
- Two studies specified that patients completed their treatment without interruption. One study reported that two patients did not complete the prescribed treatment. Other studies did not include specific statements regarding treatment interruption or discontinuation.

Subgroups

- No evidence suggesting that subgroups of patients may benefit from PBT more than the wider population was identified. In one retrospective comparison that included 871 PBT patients there was no significant association between PBT and overall survival for subgroups of patients based on tumour side, quadrant location, type of surgery (mastectomy vs breast conserving), node positivity, N2-N3 positivity or the inclusion of lymph node irradiation. In one case series adverse events were reported separately for patients who received PBT to the breast (n=27) or chest wall (n=66). However, no significance tests comparing breast and chest wall radiotherapy were reported.

Cost effectiveness

- One study compared the cost effectiveness of PBT and photon radiotherapy.

[12] Not further defined

[13] Assessed by the Brief Fatigue Inventory. This 9-item self-reported questionnaire is scored on a scale of 0 '*no fatigue*' to 10 '*as bad as you can imagine*'. An average total score was calculated for 8 of the 9 items. The 9th item was reported separately

- At a threshold of $50,000/ quality-adjusted life year (QALY) (£40,102[14]), PBT was not cost effective for women without cardiac risk factors compared to photon radiotherapy. There were some scenarios (e.g. women aged 50 years receiving a mean heart dose of 9Gy and women aged 60 years receiving a mean heart dose of 10Gy) where PBT was cost effective at this threshold compared to photon radiotherapy for women with one or more cardiac risk factors.
- At a threshold of $100,000/ QALY (£80,205) there were scenarios (based on woman's age and mean radiotherapy heart dose) where PBT was cost effective compared to photon radiotherapy for women with and without cardiac risk factors.

Conclusion

- Three retrospective comparative studies were identified which assessed clinical or safety outcomes for PBT compared to photon radiotherapy for breast cancer. However, these studies reviewed outcomes for patients who had received PBT or radiotherapy treatments rather than prospectively randomising patients to a treatment. In all three studies there were significant differences between the groups at baseline which may have had a confounding effect on the outcomes reported. Other limitations include small numbers of patients and follow-up durations that may be insufficient to assess the effectiveness of some outcomes. The ten small case series do not provide any information on the effectiveness and safety of PBT compared to photon radiotherapy.
- None of the studies identified were conducted in the UK. It is not clear how generalisable the findings are to current UK NHS clinical practice.
- The cost effectiveness model used a societal perspective (rather than direct costs) and a lifetime horizon ending at patient death or age 100 years. This, in addition to the fact that the willingness to pay thresholds used are higher than the threshold that is commonly used by NICE in the UK (£20,000 to £30,000), suggest that the findings have limited applicability to the NHS in England.
- The low quality evidence identified provides little information to answer the questions posed in this review. Prospective, comparative, randomised controlled studies with long follow-up are required to provide more robust evidence on the effectiveness and safety of PBT compared to photon radiotherapy in patients with breast cancer.

3 Methodology

- The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Commissioning Products' (2016).
- A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) to be included in this review was prepared by NHS England's Policy Working Group for the topic (see section 9 for PICO).
- The PICO was used to search for relevant publications in the following sources: Medline, Embase and Cochrane Library (see section 10 for search strategy).
- The search dates for publications were between 1st January 2009 and 1st August 2019.
- The titles and abstracts of the results from the literature searches were assessed using the criteria from the PICO. Full text versions of papers which appeared potentially useful were obtained and reviewed to determine whether they were appropriate for inclusion.

[14] Conversions from US dollars to UK pounds were calculated in September 2019

- The standard methodology for these rapid evidence reviews is to select the highest quality papers which match the PICO for inclusion using established hierarchy of evidence criteria[15]. However, on instruction from NHS England, we have also included non-comparator studies of PBT for breast cancer in this review.
- Physics planning papers such as dosimetric planning studies were not eligible for inclusion in the review as specified by the PICO criteria.
- In response to a query, NHS England confirmed that studies on PBT re-irradiation are out of scope for this review.
- Although systematic reviews were identified in the search (e.g. Verma et al 2016) these included both studies that did and did not meet the PICO. Therefore individual studies were included in this review in preference to the published systematic reviews.
- Evidence from all papers included was extracted and recorded in evidence summary tables, critically appraised and their quality assessed using the National Service Framework for Long Term Conditions (NSF-LTC) evidence assessment framework (see section 7).
- The body of evidence for individual outcomes identified in the papers was graded and recorded in grade of evidence tables (see section 8).

4 Results

Fourteen studies (three retrospective comparisons, ten case series and one cost effectiveness study) were identified for inclusion in this evidence review. No studies reported a controlled comparison of PBT and photon radiotherapy.

One retrospective comparison included 724,492 patients (Chowdhary et al 2019). The other two retrospective comparisons included 86 and 129 patients respectively (DeCesaris et al 2019, Teichman et al 2018). Sample sizes in the ten case series ranged from ten to 100. Six of these were prospective case series (Luo et al 2019, Smith et al 2019, Bradley et al 2016, Bush et al 2014, Chang et al 2013, MacDonald et al 2013). Four were retrospective case series (Liang et al 2018, Ovalle et al 2018, Verma et al 2017, Cuaron et al 2015). A cost effectiveness study was also included (Mailhot Vega et al 2017). Full details of the study designs and outcomes are summarised in the evidence tables in section 7.

1. In people undergoing adjuvant radiotherapy for breast cancer, what is the clinical effectiveness of proton beam therapy compared with photon radiotherapy?

No controlled comparative studies were identified to help answer this question. Two of the three retrospective studies comparing PBT and photon radiotherapy reported outcomes relating to clinical effectiveness (Chowdhary et al 2019, Teichman et al 2018). In addition, five of the ten case series on PBT included in this review reported clinical effectiveness outcomes (Luo et al 2019, Verma et al 2017, Cuaron et al 2015, Bush et al 2014, Chang et al 2013).

<u>Overall survival/ mortality</u>
Overall survival was reported in one retrospective comparison (Chowdhary et al 2019) and three case series (Luo et al 2019, Bush et al 2014, Chang et al 2013). Mortality was reported in one case series (Verma et al 2017). 95% confidence intervals are provided where reported.

[15] https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/

In Chowdhary et al (2019) (n=724,492), five-year overall survival was 91.9% for PBT patients (n=871) and 88.9% for photon radiotherapy patients (n=723,621). PBT was not associated with overall survival in multivariate analysis[16] (HR 0.85 (95%CI 0.68 to 1.07), p=0.168).

The three case series reported overall survival of 97.2% at a median follow-up of 35 months (Luo et al 2019, n=42), 95.0% at a median follow-up of five years (Bush et al 2014, n=100) and 100% at a median follow-up of 59 months (Chang et al 2013, n=30). In Verma et al (2017) (n=91) mortality was 7% at a median follow-up of 15.5 months.

Disease progression

A range of outcomes relating to local, regional or distant disease progression were reported in the case series. These included disease free survival[17] (Bush et al 2014), disease failure[18] (Verma et al 2017), loco-regional disease free survival (Luo et al 2019, Bush et al 2014), loco-regional recurrence (Chang et al 2013), metastasis free survival (Luo et al 2019) and distant metastasis (Cuaron et al 2015, Chang et al 2013). 95% confidence intervals are provided where reported.

Disease free survival was 94% at a median follow-up of five years (Bush et al 2014, n=100). In Verma et al (2017) (n=91) 13% had disease failure at a median follow-up of 15.5 months. This consisted of ten patients with distant recurrence, four patients with loco-regional recurrence and two patients with both distant and loco-regional recurrence.

Loco-regional disease free survival was reported as 96% at a median follow-up of 35 months (Luo et al 2019, n=42) and 97% (95%CI 93% to 100%) at a median follow-up of five years (Bush et al 2014, n=100). In Chang et al (2013) (n=30) there were no cases of loco-regional recurrence at a median follow-up of 59 months.

Metastasis free survival was 84.1% at a median follow-up of 35 months (Luo et al 2019, n=42). In Cuaron et al (2015) (n=30) 3% developed distant metastasis at a median follow-up of 9.3 months. There were no cases of distant metastasis at a median follow-up of 59 months in the case series by Chang et al (2013) (n=30).

Physician-rated cosmetic outcome[19]

Physician-rated cosmetic outcome was reported in two case series (Bush et al 2014, Chang et al 2013).

The proportion of physicians reporting an '*excellent*' or '*good*' cosmetic outcome was approximately 95%[20] from baseline to a median follow-up of five years (Bush et al (2014, n=100). In Chang et al (2013) (n=30) the proportion of physician-rated cosmetic outcomes rated '*excellent*' or '*good*' were: 84% at the end of radiotherapy (n=30), 80% at two months (n=30), 84% at six months (n=30), 77% at one year (n=30), 75% at two years (n=27) and 69% at three

[16] Adjusted for factors including age, race, insurance status, comorbidity, treatment facility type, income, residence location, education, tumour side, stage, receptor status, chemotherapy, endocrine therapy, type of surgery and year of diagnosis

[17] Not further defined

[18] Including loco-regional recurrence and distant disease

[19] In Chang et al (2013) physician-rated cosmetic outcome was assessed by global cosmetic result, appearance of the surgical scar, breast size, breast shape, skin colour and location and shape of the areola and nipple. This was assessed on a 4-point scale where 0 = '*excellent result (no difference)*', 1 = '*good result (small difference)*', 2 = '*fair result (moderate difference)*', 3 = '*poor result (large difference)*'. Percentage of breast retraction was also assessed by comparing the lateral and vertical displacement of the nipple in the treated breast compared to the untreated breast. In Bush et al this outcome was assessed by the Harvard Cosmesis Scale which rates cosmetic result as 4 = '*excellent*', 3 = '*good*', 2 = '*fair*' or 1 = '*poor*'

[20] These data were presented graphically in the study and precise figures were not reported

years (n=23). There was a statistically significant increase in mean percentage breast retraction over time from 10.5% at the end of treatment to 15.3% at three years (p=0.002).

Patient-reported cosmetic outcome[21]/ body image[22]

Patient-reported cosmetic outcome was reported in one retrospective comparison (Teichman et al 2018) and one case series (Bush et al 2014). Teichman et al (2018) also reported body image.

The mean (standard deviation (SD)) cosmetic outcome was statistically significantly better for PBT patients (n=69) than photon radiotherapy patients (n=56) (3.40 (0.75) vs 2.44 (0.96), p<0.001) at a median of 6.5 years post-diagnosis (Teichman et al 2018). In the case series by Bush et al (2014) (n=100) the proportion of PBT patients reporting an '*excellent*' or '*good*' cosmetic outcome was between approximately 90% and 95%[20] from baseline to a median follow-up of five years.

The mean (SD) body image was statistically significantly better for PBT patients (n=72) than photon radiotherapy patients (n=57) (12.04 (3.75) vs 13.91 (5.25), p<0.03) at a median of 6.5 years post-diagnosis (Teichman et al 2018).

Patient-reported treatment outcome[23]/ general perspective[24]

Patient-reported treatment outcome (cosmetic, pain, functionality and oedema) and general perspective were reported in one retrospective comparison only (Teichman et al 2018). Standard deviation was not reported for these outcomes.

In this study, the mean cosmetic subdomain score was statistically significantly better for PBT patients (n=72) than photon radiotherapy patients (n=57) (1.45 vs 1.88, p<0.001) at a median of 6.5 years post-diagnosis. However, the mean pain subdomain score was statistically significantly worse with PBT (1.42 vs 1.25, p<0.005). There was no significant difference in the functionality subdomain score (1.11 vs 1.17, p=0.311) or the oedema subdomain score (1.07 vs 1.12, p=0.526). The study authors also created a weighted score based on the average of the three questions that patients thought were most important. This was statistically significantly better for PBT than photon radiotherapy (1.84 vs 2.55, p<0.001).

The mean scores on general perspective were statistically significantly better for PBT patients (n=72) than photon radiotherapy patients (n=57) for five (of nine) questions at a median of 6.5 years post-diagnosis. These were '*happy with treatment choice*' (4.92 vs 4.20, p<0.001), '*skin "felt different" since treatment*' (1.22 vs 1.95, p<0.001), '*changed attitude about sex*' (1.41 vs 1.94, p=0.012), '*breast cancer changed views of "myself and body*"' (1.57 vs 2.16, p=0.008) and '*worry about "disease coming back*"' (2.31 vs 3.27, p<0.001). However, the mean score was statistically significantly worse with PBT for one question: '*skin quality during treatment*' (1.50 vs 2.82, p<0.001). There was no significant difference for three questions: '*changed how I live my daily*

[21] Assessed by the Harvard Cosmesis Scale which rates cosmetic result as 4 = '*excellent*', 3 = '*good*', 2 = '*fair*' or 1 = '*poor*'

[22] Assessed by the Body Image Scale. A 10-item self-reported questionnaire assessing feelings about appearance and changes which may have resulted from a disease or treatment during the prior week. Scored from 1 to 4 with higher scores indicating more dissatisfaction/ negative feelings, where 1 = '*not at all*', 2 = '*a little*', 3 = '*quite a bit*', 4 = '*very much*'

[23] Assessed by the Breast Cancer Treatment Outcome Scale. A 22-item questionnaire evaluating functional and cosmetic outcome, reported as 4 subdomains: cosmetic, breast specific pain, functionality and oedema. Items are scored from 1 to 4 based on any difference between the treated and untreated breast where 1 = '*none*', 2 = '*slight*', 3 = '*moderate*' and 4 = '*large (major)*'

[24] Assessed by 9 questions generated by the study authors which were scored on a 5-point scale from 1 = '*not at all*' to 5 = '*very much*'

life' (2.00 vs 2.30, p=0.197), '*role of spirituality/ religion*' (4.35 vs 4.00, p=0.116) and '*upper arms/ mobility issues*' (1.19 vs 1.30, p=0.348).

Quality of life[25]
Quality of life was reported in one case series (Chang et al 2013, n=30).

There were no significant differences before PBT treatment and after the last day of radiotherapy for any of the six functional subscales or any of the nine symptom subscales on the general quality of life questionnaire. There were also no significant differences before and after treatment for any of the three functional subscales or any of the three symptom subscales on the breast cancer specific quality of life questionnaire. For quality of life scores see section 7.

2. In people undergoing adjuvant radiotherapy for breast cancer, what is the safety of proton beam therapy compared with photon radiotherapy?

No controlled comparative studies were identified to help answer this question. Two of the three retrospective studies comparing PBT and photon radiotherapy reported outcomes relating to safety (DeCesaris et al 2019, Teichman et al 2018). In addition, all ten of the case series included in this review reported safety outcomes (Luo et al 2019, Smith et al 2019, Liang et al 2018, Ovalle et al 2018, Verma et al 2017, Bradley et al 2016, Cuaron et al 2015, Bush et al 2014, Chang et al 2013, MacDonald et al 2013). Studies reporting a range of adverse events are reported first. Studies that focused on specific safety outcomes such as fatigue, skin toxicity or complications for PBT patients who had immediate reconstruction following mastectomy are reported separately.

Adverse events
Adverse events were reported in nine case series (Luo et al 2019, Smith et al 2019, Ovalle et al 2018, Verma et al 2017, Bradley et al 2016, Cuaron et al 2015, Bush et al 2014, Chang et al 2013, MacDonald et al 2013).

No Grade 4 (life threatening) or Grade 5 (death) adverse events were reported.

Although Grade 3 (severe) adverse events were not reported in two case series (Cuaron et al 2015, n=30), Bush et al 2014, n=100), seven case series did report grade 3 adverse events. These included one case of pneumonitis more than 90 days after radiotherapy (Luo et al 2019, n=42), two cases of radiation dermatitis (Smith et al 2019, n=51) with median follow-up of 19 months, five cases of dermatitis and one case of breast/ chest wall pain (Verma et al 2017, n=91) with median follow-up of 15.5 months, three cases of dermatitis where median follow-up was not reported (Bradley et al 2016, n=10), one case of wet desquamation at two months follow-up (Chang et al 2013, n=30) and one case of fatigue during radiotherapy (MacDonald et al 2013, n=12). In addition, at six months follow-up, Ovalle et al (2018) reported that 5% of 43 patients who received PBT experienced moderate/ severe hyperpigmentation and two of the 11 cases of retraction or significant asymmetry between breasts were considered moderate or severe. Other

[25] Assessed by the European Organization for Research and Treatment of Cancer 30 Quality of Life Questionnaire (EORTC QLQ-C30) and the EORTC breast cancer specific questionnaire (EORTC QLQ-BR23). These are scored out of 100 with higher functional scores and lower symptoms scores indicating better quality of life. The EORTC QLQ-C30 includes 6 functional subscales (global health status, physical, role, emotional cognitive and social functioning) and 9 symptom subscales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties). The EORTC QLQ-BR23 includes 3 functional subscales (body image, sexual function and future perspective) and 3 symptom subscales (systemic therapy side effects, breast symptoms and arm symptoms)

moderate or severe adverse events in this study were only reported graphically and the proportion of patients affected is not clear.

The Grade 2 (moderate) adverse events reported in case series were:

- Dermatitis (74%), skin pain (24%), oesophagitis (17%) and fatigue (2%) reported <90 days after radiotherapy (Luo et al 2019, n=42)
- Radiation dermatitis (33%) and oesophagitis (2%) with median follow-up of 19 months (Smith et al 2019, n=51)
- Dermatitis (72%), breast/ chest wall pain (29%), oesophagitis (33%) and fatigue (15%) with median follow-up of 15.5 months (Verma et al 2017, n=91). In addition, 8% developed a skin infection, 2% had uncomplicated rib fracture, and 3% had clinically evident lymphoedema (Grade not specified)
- Dermatitis (100%) and infection (10%) at an unknown median follow-up (Bradley et al 2016, n=10)[26]
- Dermatitis (71%), moist desquamation (29%), skin pain (25%) chest wall pain (4%), oesophagitis (29%) and fatigue (4%) at median follow-up of 9.3 months (Cuaron et al 2015, n=30)
- Breast oedema (3% at two and six months), erythema/ hyperpigmentation (30% at two months, 13% at six months and one year, 7% at two years and 9% at three years), wet desquamation (3% at two months) and induration (3% at six months, 7% at one year and 4% at two and three years) (Chang et al 2013, n=30). In addition two patients had rib fracture (one at six months and one at two years)
- Skin hyperpigmentation (75%) and fatigue (42%) during radiotherapy. There were no moderate adverse events at four or eight weeks follow-up (MacDonald et al 2013, n=12).

Grade 1-2 radiation dermatitis was experienced by 62% of 100 patients who received PBT in one case series (Bush et al 2014).

See section 7 for details of mild adverse events reported.

Two studies specified that patients completed their treatment without interruption (Cuaron et al 2015, Bush et al 2014). Only one study reported that two (of 91) patients did not complete the prescribed treatment, in one case due to Grade 2 dermatitis. No reason was specified for the other patient. Other studies did not included specific statements regarding treatment interruption or discontinuation.

Fatigue[27]

Fatigue was reported in one retrospective comparison (Teichman et al 2018).

In this study the mean (SD) fatigue was statistically significantly better for PBT patients (n=72) than photon radiotherapy patients (n=57) (15.3 (17.11) vs 27.25 (22.26), p<0.002) at a median of 6.5 years post-diagnosis. The authors also created a weighted score based on the average of the three questions that patients thought were most important. There was no significant difference between the groups (1.84 vs 2.55, p<0.001). The proportion of patients responding '*yes*' to the question '*have you felt unusually tired or fatigued in the last week*' was 25% for PBT (n=71) and 63% (n=51) for photon radiotherapy. No significance test was reported.

[26] The population of this study also included patients who had received combined proton-photon radiotherapy. Only adverse events that are known to have been experienced by PBT only patients are reported here. For further details see section 7

[27] Assessed by the Brief Fatigue Inventory. This 9-item self-reported questionnaire is scored on a scale of 0 '*no fatigue*' to 10 '*as bad as you can imagine*'. An average total score was calculated for 8 of the 9 items. The 9th item was reported separately

Skin toxicity[28]

Skin toxicity was reported in one retrospective comparison (DeCesaris et al 2019) and one case series (Liang et al 2018).

There were no Grade 4 or Grade 5 skin toxicities reported and there was no significant difference in acute Grade 3 radiation dermatitis between PBT (n=39) and photon (n=47) radiotherapy (5.1% vs 4.3%, p=0.848) (DeCesaris et al 2019, n=86). Radiation dermatitis ≥ Grade 2 was statistically significantly higher with PBT (69.2% vs 29.8%, p<0.01). The highest recorded grade of radiation dermatitis was also statistically significantly higher with PBT (p=0.002). There was no significant difference in acute skin hyperpigmentation ≥ Grade 2 (7.7% vs 12.8%, p=0.502). There was also no significant difference in the highest recorded grade of skin hyperpigmentation (p=0.413). At first clinical follow-up (within eight weeks of treatment completion), there was no difference in sustained skin reactions between PBT (n=29) and photon (n=41) radiotherapy (Grade 1 radiation dermatitis 17.2% vs 19.5%, p=0.810; Grade 1 skin hyperpigmentation 65.5% vs 61.0%, p=0.698).

In a case series of 23 patients treated with PBT, 43% had Grade 3 radiation dermatitis and 100% had ≥ Grade 2 skin reactions including erythema or patchy moist desquamation confined to skin folds. Median follow-up was not reported (Liang et al 2018).

Reconstruction complications

Reconstruction complications were reported in two case series (Luo et al 2019, Smith et al 2019). These patients received PBT after a mastectomy with immediate reconstruction.

Of 26 patients who underwent PBT after immediate breast reconstruction, seven (27%) developed complications including six capsular contractures and one implant infection. Implants were removed in five patients. Median follow-up was 35 months (Luo et al 2019, n=42). In Smith et al (2019) (n=51) 39% had one or more complications at 19 months follow-up. This included 14 surgical site infections, four seromas, two flap necrosis, two late infections, one haematoma and one contracture. Eight patients had reconstruction failure (implants removed).

3. In people undergoing adjuvant radiotherapy for breast cancer, what is the cost effectiveness of proton beam therapy compared with photon radiotherapy?

One study (Mailhot Vega et al 2017) considered the cost effectiveness of PBT compared to photon radiotherapy for breast cancer. This study modelled scenarios for which PBT would potentially be cost effective compared to photon radiotherapy using a societal perspective across a lifetime horizon (up to 100 years). This approach is likely to favour PBT, and is inconsistent with the direct approach usually used to estimate cost effectiveness of interventions for the NHS.

[28] Assessed by the Common Terminology Criteria for Adverse Events Version 4.0. On this scale Grade 1 = '*mild*', Grade 2 = '*moderate*', Grade 3 = '*severe or medically significant but not immediately life-threatening*', Grade 4 = '*life-threatening consequences*' and Grade 5 = '*death related to adverse event*' (https://www.eortc.be/services/doc/ctc/ctcae_4.03_2010-06-14_quickreference_5x7.pdf)

- At a threshold of $50,000/ QALY (£40,102[29]), PBT was not cost effective for women without cardiac risk factors compared to photon radiotherapy. This remained the case following sensitivity analysis.
- For a subset of the women who had one or more cardiac risk factors, the model indicates that at a threshold of $50,000/ QALY (£40,102), PBT was cost effective compared to photon radiotherapy. The criteria for these subsets were based on age and the mean radiotherapy heart dose (e.g. women aged 50 years receiving a mean heart dose of 9Gy and women aged 60 years receiving a mean heart dose of 10Gy).
- At a threshold of $100,000/ QALY (£80,205) there were scenarios (based on woman's age and mean radiotherapy heart dose) where PBT was cost effective compared to photon radiotherapy for both women with and without cardiac risk factors.

4. From the evidence selected, are there any subgroups of patients that may benefit from proton beam therapy more than the wider population of interest (such as, but not limited to, people receiving radiotherapy to breast/ chest wall and internal mammary nodes and people with pectus excavatum)?

Some studies reported results for subgroups of patients. However no evidence suggesting that subgroups of patients may benefit from PBT more than the wider population was identified. For example, in Chowdhary et al (2019) there was no significant association between PBT and overall survival for subgroups of patients based on tumour side, quadrant location, type of surgery (mastectomy vs breast conserving), node positivity, N2-N3 positivity or the inclusion of lymph node irradiation (see section 7 for details). In the case series by Verma et al (2018) adverse events were reported separately for patients who received PBT to the breast (n=27) or chest wall (n=66). However, no significance tests comparing breast and chest wall radiotherapy were reported. The only Grade 3 adverse event for breast radiotherapy patients was dermatitis (7%). Grade 3 adverse events for chest wall radiotherapy patients included dermatitis (5%) and pain (2%). Grade 2 adverse events for breast radiotherapy patients included dermatitis (56%), pain (52%), oesophagitis (30%) and fatigue (7%). Grade 2 adverse events for chest wall radiotherapy patients included dermatitis (79%), pain (20%), oesophagitis (33%) and fatigue (5%). Median follow-up was 15.5 months.

5 Discussion

Only low quality evidence was identified in relation to the effectiveness of PBT compared to photon radiotherapy in patients with breast cancer.

Three retrospective comparative studies were identified which assessed clinical or safety outcomes for PBT compared to photon radiotherapy for breast cancer. However, these studies retrospectively reviewed patients who had received PBT or photon radiotherapy treatments rather than prospectively randomising patients to a treatment. The study design introduces the possibility of selection bias in the choice of treatment and completeness of the information reported. There were differences in the type and dosage of PBT or photon radiotherapy received by patients within these studies. In all three studies there were significant differences between the patient groups at baseline which may have had a confounding effect on the outcomes reported. These included differences in ethnicity, factors such as income or insurance status and factors such as cancer stage and tumour location.

[29] Conversions from US dollars to UK pounds were calculated in September 2019

The ten case series on PBT identified were all small studies with samples sizes ranging from 10 to 100 patients.

None of the studies identified were conducted in the UK. It is not clear how generalisable the findings are to the UK. Twelve of the thirteen included studies examining clinical effectiveness were from the US. The remaining study was from Korea. One of the retrospective studies used data from a national database (US). The other studies, when stated, were from a single centre. The year of treatment, when stated, varied ranging from 2003 to 2017. Treatment practices and protocols are likely to have changed over time and may not reflect current practice.

A range of outcomes were reported by the studies. These included objective outcomes such as survival and the use of standardised assessment scales to assess outcomes such as adverse events. From the comparative evidence available there was no evidence of a difference in overall survival between PBT and photon radiotherapy. There was some evidence that PBT is associated with higher acute radiation dermatitis, but there was no evidence of a difference in sustained skin reactions at clinical follow-up within eight weeks of treatment. However it should be noted that data from clinical follow-up were only available for 74% and 87% of PBT and photon patients respectively. Most of the evidence relating to objective outcomes comes from case series of PBT which do not provide any information on the effectiveness of PBT compared to photon radiotherapy.

Other outcome measures comparing PBT and photon radiotherapy in one of the retrospective comparisons (Teichman et al 2018) relied on the self-report of patients to assess treatment outcomes, body image, cosmetic outcomes and quality of life. These outcomes could be subject to response bias. For example, the study authors noted that the majority of PBT patients had received their treatment during a clinical trial whereas photon radiotherapy patients had received the conventional treatment for that time. This may have had a confounding effect on attitudes to the treatment received and perceptions of outcomes if patients felt that they were receiving the most advanced treatment available for their disease. Additional differences in the type and delivery of radiotherapy between the two groups may also have had a confounding effect on the outcomes reported. For example in this study, PBT patients received partial breast radiotherapy over 10 days and photon radiotherapy patients received whole breast radiotherapy over six weeks.

Although some studies had median follow-up of approximately five years, this may not have been long enough to assess the impact of PBT on survival, disease progression or potential longer term treatment toxicities.

The PICO commissioned for this evidence review did not include any restrictions on the type of adjuvant proton radiotherapy received by patients and included any type or severity of breast cancer. The studies included demonstrated considerable heterogeneity in the study populations and treatments received. For example, some studies had inclusion criteria that specified a particular cancer stage, tumour size or excluded patients with metastatic disease. In other studies no such specifications were made. Most studies reported the proportion of patients who also received chemotherapy, in others this was not reported or in the case of Teichman et al (2018), patients were excluded if they had received chemotherapy. The type of PBT received is likely to have reflected the technology available at the centre at the time of treatment. However the variation between the studies introduces additional uncertainty about the applicability of the results to current UK NHS clinical practice.

No clinical studies compared outcomes to identify subgroups of patients who may benefit from PBT more than the wider population of interest. Well-constructed clinical trials that accurately define such subgroups are required.

One cost effectiveness study modelled patient selection factors and scenarios for which PBT may be cost effective compared to photon radiotherapy due to differences in age and mean heart dose. This considered cost effectiveness at two willingness to pay thresholds ($50,000/ QALY (£40,102) and $100,000/ QALY (£80,205). These are higher than the threshold commonly used by NICE in the UK (£20,000 to £30,000) which limits the study's applicability to the UK NHS context. The model used a lifetime horizon ending at patient death or age 100 years, which may make intervention appear more cost effective than if a lower, more realistic, life-expectancy had been applied. The model also used a societal perspective rather than direct costs which are more typically used to assess cost effectiveness in the UK. At the lower $50,000/ QALY threshold, PBT was not cost effective compared to photon radiotherapy for any women who did not have cardiac risk factors[30]. There were some scenarios (based on woman's age and mean radiotherapy heart dose) where PBT was cost effective at the higher threshold ($100,000/ QALY) compared to photon radiotherapy for women with one or more cardiac risk factors. The study did not model outcomes for male patients with breast cancer. The results of this cost effectiveness study should be treated with caution. The 100 year life expectancy, the inclusion of societal costs and the high willingness to pay thresholds mean that the results are not generalisable to the NHS in England.

Although some study authors declared an association with a manufacturer, studies generally stated that there were no conflicts of interest suggesting a low risk of bias in that respect.

6 Conclusion

The low quality evidence identified provides little information to answer the questions posed in this review.

The retrospective design of the three comparative studies identified limit any conclusions that can be drawn about the effectiveness of PBT compared to photon radiotherapy. The ten case series included do not provide any information on the effectiveness or safety of PBT compared to photon radiotherapy. The applicability of the evidence identified to current UK NHS clinical practice is unclear.

There is some modelling evidence that PBT might be cost effective compared to photon radiotherapy in some scenarios. However, the applicability of this finding to the UK NHS context is questionable due to the modelling approach, the assumptions used and the application of a higher cost effectiveness threshold than is used by the NHS in England.

Prospective, comparative, randomised controlled studies with long follow-up are required to provide more robust evidence on the effectiveness and safety of PBT compared to photon radiotherapy in patients with breast cancer.

[30] Cardiac risk factors was not defined by the study authors

7 Evidence Summary Table

For abbreviations see list after each table

a) Use of proton beam therapy (PBT) vs. photon radiotherapy									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Chowdhary et al 2019	S2 Retrospective comparison using a national cancer database US patients treated between 2004 and 2014	n=724,492 Patients with breast cancer treated with adjuvant radiotherapy to breast or chest wall ± regional lymph nodes following surgery Patients were excluded if they had metastatic disease at diagnosis, if survival outcomes were not recorded, if they had received radiotherapy to a site other than the breast, or any radiotherapy prior to surgery	PBT (not further defined): n=871 Non-proton radiotherapy i.e. photon radiotherapy ± electrons: n= 723,621 Median total radiation dose (range not reported): • PBT: 60.0 Gy • Photon: 60.4 Gy Patients were excluded if they received a dose of <39 or >70 Gy. Patients were excluded if they had received non-external beam radiotherapy (i.e. brachytherapy, intraoperative radiotherapy, stereotactic radiosurgery or radioisotopes)	Primary Clinical effectiveness	Overall survival	5 year overall survival: • PBT: 91.9% • Photon: 88.9% 95%CI not reported Overall survival not associated with PBT in multivariate analysis (HR 0.85 (95%CI 0.68 to 1.07), p=0.168) No significant association for PBT in multivariate analysis with stratification for subgroups of patients for[31]: • Left-side tumour: HR 0.78 (95%CI 0.57 to 1.08), p=0.140 • Right-side tumour: HR 0.93 (95%CI 0.68 to 1.28), p=0.671 • Inner-quadrant: HR 0.60 (95%CI 0.28 to 1.25), p=0.173 • Outer quadrant: HR 0.48 (95%CI 0.15 to 1.48), p=0.199 • Mastectomy: HR 0.79 (95%CI 0.60 to 1.04), p=0.095 • Breast conserving surgery: HR 1.03 (95%CI 0.69 to 1.54), p=0.886 • Node positive: HR 1.07 (95%CI 0.77 to 1.50), p=0.680 • Node negative: HR 0.75 (95%CI 0.55 to 1.02), p=0.066	7	Direct	This paper primarily focused on utilisation patterns for PBT. This is out of scope for this review. Only outcomes relating to clinical effectiveness are reproduced. There were a number of differences between the groups at baseline in areas which may be confounding factors for overall survival. The multivariate analysis reported adjusted for factors including age, race, insurance status, comorbidity, treatment facility type, income, residence location, education, tumour side, stage, receptor status, chemotherapy, endocrine therapy, type of surgery and year of diagnosis. With this adjustment, there was no significant difference in overall survival between groups nor any significant advantage for PBT for subgroups. The authors noted that the median follow-up of 62 months may not have been long enough for some treatment-related toxicities e.g. cardiac toxicities, to affect overall survival. The median follow-up was significantly longer for PBT patients with a 12 month difference in the median for each group. The retrospective comparison performed used data from a national database of patients treated in the US between 2004 and 2014. The applicability to current UK NHS clinical practice is unclear. The retrospective design introduces

[31] The authors specified that the first listed variable in these subgroups is this group considered at more risk

a) Use of proton beam therapy (PBT) vs. photon radiotherapy									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		Median age not reported % female: 99.4% Baseline characteristics were similar between groups for age and education status Proton patients had higher percentages of Caucasian race, private insurance, median income >$63,000, treatment at an academic facility, metropolitan residence, West (geographic)location, group stage 0-1 patients, mastectomy and left-sided tumours (p<0.05)	Rates of lymph node irradiation were similar between groups Proportion of patients receiving chemotherapy not reported Median follow-up 62.2 months (range not reported) Median follow-up was significantly longer for PBT (74.6 months) vs photon (62.2 months) patients (p<0.001)			• N2-N3 positive: HR 1.04 (95%CI 0.65 to 1.65), p=0.880 • N2-N3 negative: HR 0.81 (95%CI 0.63 to 1.05), p=0.118 • Breast and lymph node irradiation: HR 0.94 (95%CI 0.61 to 1.44), p=0.767 • Breast irradiation only: HR 0.82 (95%CI 0.63 to 1.07), p=0.143			the possibility of selection bias in the completeness of the information reported. The authors stated that there were no conflicts of interest

a) Use of proton beam therapy (PBT) vs. photon radiotherapy									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
DeCesaris et al 2019	S2 Retrospective comparison of patients treated at 1 US centre between 2015 and 2017	n=86 Patients >18 years with invasive breast cancer undergoing adjuvant radiation therapy to the breast or chest wall ± regional lymph nodes following lumpectomy or mastectomy. Patients with weekly on-treatment visit documentation of acute treatment related toxicities Patients excluded if they had a history of breast or chest wall	PBT (pencil-beam scanning): n=39 Photon radiotherapy: n=47 Median dose 60Gy (range 45 to 70) Significantly more photon patients had initial fields treated in 2.0Gy fractions, with more PBT patients treated in 1.8 Gy fractions (p=0.001) Regional node irradiation • PBT: 95% • Photon: 83% Neoadjuvant chemotherapy • PBT: 54% • Photon: 53%	Safety	Skin toxicity Assessed by the Common Terminology Criteria for Adverse Events, version 4.0[32]	No grade 4 or 5 radiation dermatitis No significant difference in grade 3 radiation dermatitis between PBT and photon (5.1% vs 4.3%, p=0.848) **Highest recorded grade of radiation dermatitis:** Significantly higher with PBT (p=0.002) **Acute radiation dermatitis ≥ grade 2** • PBT: 27 (69.2%) • Photon: 14 (29.8%) Significantly higher with PBT (p<0.01) **Highest recorded grade of skin hyperpigmentation:** No significant difference between PBT and photon radiotherapy (p=0.413) **Skin hyperpigmentation ≥ grade 2** • PBT: 3 (7.7%) • Photon: 6 (12.8%) No significant difference between PBT and photon radiotherapy (p=0.502) **At first clinical follow-up** (within 8 weeks of treatment completion) there was no difference in sustained skin reactions between PBT (n=29) and photon radiotherapy (n=41): • Grade 1 radiation dermatitis (17.2% vs 19.5%, p=0.810)	7	Direct	The authors stated that the observed difference in ethnicity between groups at baseline may have reflected patient self-referral and insurance type rather than physician treatment selection. Toxicity was assessed on a weekly basis during treatment. Toxicities were primarily scored by the same treating physician for both photon and proton treatments. The highest recorded incidence of skin toxicities was included for each patient. Data from first clinical follow-up assessment following treatment was available for 74% of proton patients and 87% of photon patients. Dosimetric analysis conducted by the authors is not reproduced. This retrospective comparison used data from 1 US centre from between 2015 and 2017. The applicability to current UK NHS clinical practice is unclear. The retrospective design introduces the possibility of selection bias in the completeness of the information reported. One author declared an association with a manufacturer. No other conflicts of interest were declared

[32] Radiation dermatitis scored as grade 1 = "*faint erythema or dry desquamation*"; grade 2 = "*moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate oedema*"; grade 3 = "*moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion*"; grade 4 = "*life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated*"; grade 5 = "*death*"
Skin hyperpigmentation scored as grade 1 = "*hyperpigmentation covering <10% body service area; no psychological impact*"; grade 2 = "*hyperpigmentation covering >10% body service area; psychological impact*". Grades 3 to 5 not applicable for this outcome (DeCesaris et al 2019)

a) Use of proton beam therapy (PBT) vs. photon radiotherapy									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		irradiation, metastatic disease or had received hypofractionated radiotherapy Median age 53 years (range 24-78) % female: • Proton: 97.4% • Photon: 97.9% Tumour side not reported. Bilateral breast/ chest wall irradiation: • Proton: n=2 • Photon: n=3 Baseline characteristics were similar between groups for age, sex, BMI, current smokers, diabetes and ECOG score A higher proportion of photon	Concurrent chemotherapy • PBT: 2% • Photon: 38% Disease status (primary vs recurrent), chemotherapy use, type of surgery, inclusion of regional nodes, cancer stage, skin involvement at presentation, total radiation dose, inclusion of boost, total boost dose and boost dose per fraction was similar between groups Median follow-up not reported			• Grade 1 skin hyperpigmentation (65.5% vs 61.0%, p=0.698)			

a) Use of proton beam therapy (PBT) vs. photon radiotherapy									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		patients were former smokers (51.1% vs 28.2%, p=0.032). There was also a significant difference in ethnicity between the groups (p=0.04) White • PBT: 59.0% • PBT: 31.9% Black • PBT: 28.2% • Photon: 63.8% Other • PBT: 12.8% • Photon: 4.3%							
Teichman et al 2018	S2 Retrospective comparison of patients treated at 1 US centre between 2003 and 2012 Data collected via self-	n=129 Patients aged >40 at diagnosis with stage 0-2 breast cancer and tumour size ≤3 cm, treated with adjuvant radiotherapy after	PBT (partial breast proton therapy): n=72 Photon radiotherapy (whole breast irradiation using x-rays): n=57 PBT delivered as 40 cobalt-gray	Primary Clinical effectiveness	Patient-reported cosmetic result Assessed by Harvard Cosmesis Scale[34]	Mean (SD) score • PBT (n=69): 3.40 (0.75) • Photon (n=56): 2.44 (0.96) Significantly better cosmetic result with PBT (p<0.001)	4	Direct	Data were collected through surveys sent to 180 patients who were alive and disease-free 5 years or more after diagnosis. 142 patients replied (a 79% response rate) of which 13 were excluded due to bilateral disease, disease recurrence, recently diagnosed stage 4 disease and serious medical comorbidities. The proportion of non-responders that received proton or photon radiotherapy was not specified.
				Primary Clinical effectiveness	Patient-reported treatment outcome	**Cosmetic mean score** • PBT: 1.45 • Photon: 1.88 SD not reported			

34 A single-item question rating cosmetic result as 4 = '*excellent*', 3 = '*good*', 2 = '*fair*' or 1 = '*poor*'

a) Use of proton beam therapy (PBT) vs. photon radiotherapy									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
	reported survey	lumpectomy who were disease-free survivors >5 years post-diagnosis Median age (years): • PBT: 72.5 (range 53 to 94) • Photon: 70 (range 46 to 86) % female: 100% Tumour side PBT: • Left: 57% • Right: 43% Photon: • Left: 51% • Right: 49% Baseline characteristics were similar between groups for age, employment, education, marital status,	equivalent in 10 daily fractions Photon radiotherapy delivered as 50 Gy x-rays to the whole breast followed by a 10 Gy boost to the tumour bed, 5 days per week for approximately 6 weeks Patients were excluded if they had received chemotherapy Data collected a median of 6.5 years post-diagnosis. Approximately 4 years to approximately 10 years post-treatment		Assessed by the Breast Cancer Treatment Outcome Scale (BCTOS)[35]	Significantly better cosmetic result with PBT (p<0.001) **Breast specific pain mean score** • PBT: 1.42 • Photon: 1.25 SD not reported Significantly worse pain result with PBT (p=0.005) **Functionality** • PBT: 1.11 • Photon: 1.17 SD not reported No significant difference between PBT and photon radiotherapy (p=0.311) **Oedema** • PBT: 1.07 • Photon: 1.12 SD not reported No significant difference between PBT and photon radiotherapy (p=0.526) **Weighted BCTOS score[36]** • PBT: 1.84 • Photon: 2.55 SD not reported Significantly better result with PBT (p<0.001)			The number of patients reported for an outcome is indicated where this was less than all respondents. Standard deviation was reported for some, but not all mean scores. The survey also included a 20-item questionnaire, the Medical Outcomes Study Short Form Survey. Although the paper included text suggesting that there were significant differences between the groups on 6 of these 20 questions no detail specifying the mean scores or direction of the significance was reported. Therefore this outcome has not been reproduced. The authors stated that most of the PBT patients were drawn from the same study reported by Bush et al (2014) (see below). The study authors note that all but 2 of the PBT patients received their treatment during a clinical trial, whereas the photon patients received the conventional treatment at that time. This may have had a confounding effect on attitudes to the treatment received or perceptions of outcomes e.g. if PBT patients felt that they were receiving the most advanced treatment available for their disease. The differences in treated volume (partial breast protons vs whole breast photons) and delivery of radiotherapy (10 days vs 6 weeks) may also have had a confounding effect on the outcomes reported.
				Primary Clinical effectiveness	Body image	**Total score mean (SD)** • PBT: 12.04 (3.75) • Photon: 13.91 (5.25) Significantly better result with PBT (p<0.03)			

35 A 22-item self-reported questionnaire evaluating functional and cosmetic outcome, reported as 4 subdomains: cosmetic, breast specific pain, functionality and oedema. Items are scored from 1 to 4 based on any difference between the treated and untreated breast where 1 = '*none*', 2 = '*slight*', 3 = '*moderate*' and 4 = *'large (major*)'

[36] A weighted score was created by the study authors by asking patients to circle 3 questions they thought most important. Scores were averaged for respondents

a) Use of proton beam therapy (PBT) vs. photon radiotherapy									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		stage, tumour size, lymph node surgery, tumour side and endocrine therapy PBT patients had a higher proportion of Caucasian patients, greater time since diagnosis and more positive scores regarding convenience of care[33]			Assessed by the Body Image Scale[37]				This retrospective comparison used data from 1 US centre from between 2003 and 2012. The applicability to current UK NHS clinical practice is unclear. The retrospective design introduces the possibility of selection bias in the completeness of the information reported. The study was supported by an endowment for proton therapy research. The authors stated that there were no conflicts of interest
				Primary Clinical effectiveness	General perspective Assessed by 9 questions generated by the study authors[38]	Mean scores (SD not reported) '***Happy with treatment choice***' • PBT: 4.92 • Photon: 4.20 Significantly better with PBT (p<0.001) '***Skin quality during treatment***' • PBT: 1.50 • Photon: 2.82 Significantly worse with PBT (p<0.001) '***Skin "felt different" since treatment***' • PBT: 1.22 • Photon: 1.95 Significantly better with PBT (p<0.001) '***Changed attitude about sex***' • PBT: 1.41 • Photon: 1.94 Significantly better with PBT (p=0.012) '***Breast cancer changed views of "myself and body"***' • PBT: 1.57 • Photon: 2.16 Significantly better with PBT (p=0.008) '***Worry about "disease coming back"***' • PBT: 2.31			

[33] Assessed via questions on impact on work or home duties, daily treatment duration and distance to radiation centre
[37] A 10-item self-reported questionnaire assessing feelings about appearance and changes which may have resulted from a disease or treatment during the prior week. Scored from 1 to 4 with higher scores indicating more dissatisfaction/ negative feelings, where 1 = '*not at all*', 2 = '*a little*', 3 = '*quite a bit*', 4 = '*very much*'
[38] Each question rated on a 5-point scale from 1 = '*not at all*' to 5 = '*very much*'

a) Use of proton beam therapy (PBT) vs. photon radiotherapy									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						• Photon: 3.27 Significantly better with PBT (p<0.001) **'*Changed how I live my daily life*'** • PBT: 2.00 • Photon: 2.30 No significant difference between PBT and photon radiotherapy (p=0.197) **'*Role of spirituality/ religion*'** • PBT: 4.35 • Photon: 4.00 No significant difference between PBT and photon radiotherapy (p=0.116) **'*Upper arm/ mobility issues*'** • PBT: 1.19 • Photon: 1.30 No significant difference between PBT and photon radiotherapy (p=0.348)			
				Safety	Fatigue Assessed by the Brief Fatigue Inventory[39]	**Total score mean (SD)** (excluding 1 item) • PBT: 15.3 (17.11) • Photon: 27.25 (22.26) Significantly better with PBT (p<0.002) **Weighted score mean (SD)**[36] • PBT: 3.12 (3.19) • Photon: 3.90 (2.51) No significant difference between PBT and photon radiotherapy (p=0.531) **'*Have you felt unusually tired or fatigued in the last week*'** Proportion responding '*yes*' • PBT (n=71): 25% • Photon (n=51): 63%			

[39] A 9-item self-reported questionnaire scored on a scale of 0 '*no fatigue*' to 10 '*as bad as you can imagine*'. An average total score was calculated for 8 of the 9 items. The 9th item ('*have you felt unusually tired or fatigued in the last week*') was reported separately

a) Use of proton beam therapy (PBT) vs. photon radiotherapy									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						No significance test reported			
Mailhot Vega et al 2017	S2 Cost effectiveness study modelling patient selection factors and scenarios for which PBT would potentially be cost effective compared to photon radiotherapy due to differences in mean heart dose Data to populate the model were taken from published studies, US guidance and average Medicare reimbursements	Patients with breast cancer Model entrants could be healthy; alive with coronary heart disease (CHD) or dead The model considered women aged 40, 50 or 60 years The model included women with or without cardiac risk factors	PBT (where the average plan yielded a mean heart dose of 0.5Gy) Photon radiotherapy (mean heart dose range 1Gy to 10Gy)	Cost effectiveness	Incremental cost effectiveness ratio (ICER)	**At a threshold of $50,000/QALY (£40,102):** PBT was not cost effective for women without cardiac risk factors PBT was cost effective in 2 scenarios for women with ≥1 cardiac risk factors: • 50 years old receiving a mean heart dose of 9 Gy • 60 years old receiving a mean heart dose of 10 Gy ***Sensitivity analysis*** PBT was not cost effective for any scenarios for women with no cardiac risk factors PBT was cost effective in 3 scenarios for women with ≥1 cardiac risk factors: • 40 years old receiving a mean heart dose of 9Gy • 50 years old receiving a mean heart dose of 7Gy • 60 years old receiving a mean heart dose of 8Gy **At a threshold of $100,000/QALY (£80,205):** PBT was cost effective in 2 scenarios for women with no cardiac risk factors: • 40 years old receiving a mean heart dose of 10Gy • 50 years old receiving a mean heart dose of 9Gy PBT was cost effective in 3 scenarios for women with ≥1 cardiac risk factors: • 40 years old receiving a mean heart dose of 6Gy	5	Direct	Cardiac risk factors were not defined. The model assumed no difference in tumour control with PBT and photon radiotherapy. A five year survival rate of 94% was assumed based on US national statistics from 2014. The model assumed that differences in mean heart dose would result in different rates of major cardiac events. Costs included treatment costs (incorporating capital cost of construction, overhead, salary, land, personnel and facilities) and assuming a facility lifespan of 30 years; diagnosis and medical management of CHD; annual electrocardiogram. Costs and QALYS were discounted at an annual rate of 3%. Sensitivity analysis included percutaneous coronary intervention (PCI), chance of PCI occurring in an inpatient or outpatient setting and elevated risk of death from CHD. Conversions from US dollar to UK sterling were calculated in September 2019. Model cycles were equivalent to 1 year with simulations using a lifetime horizon ending at patient death or age 100 years. This time horizon is implausible and may make the treatment appear more cost effective than if a lower, more realistic life expectancy had been applied. The analysis used a societal perspective for 2012 US dollars. Modelling using direct costs

a) Use of proton beam therapy (PBT) vs. photon radiotherapy									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						• 50 years old receiving a mean heart dose of 5Gy • 60 years old receiving a mean heart dose of 6Gy ***Sensitivity analysis*** PBT was cost effective in 3 scenarios for women with no cardiac risk factors: • 40 years old receiving a mean heart dose of 9Gy • 50 years old receiving a mean heart dose of 7Gy • 60 years old receiving a mean heart dose of 9Gy PBT was cost effective in 3 scenarios for women with ≥1 cardiac risk factors: • 40 years old receiving a mean heart dose of 5Gy • 50 years old receiving a mean heart dose of 4Gy • 60 years old receiving a mean heart dose of 5Gy			is more typically used in the UK and would be more applicable to a UK NHS context and the thresholds commonly used by NICE to assess cost effectiveness. The results are not generalisable to a UK NHS setting due to the inclusion of indirect costs, US costs, unrealistic life expectancy and a high willingness to pay threshold. The authors stated that there were no conflicts of interest.

BCTOS – Breast Cancer Treatment Outcome Scale; BMI – body mass index; CHD – Coronary Heart Disease; CI – confidence interval; ECOG – Eastern Cooperative Oncology Group; Gy – Gray; HR – hazard ratio; ICER - Incremental Cost Effectiveness Ratio; OR – odds ratio; PBT – proton beam therapy; PCI - Percutaneous Coronary Intervention; QALY - Quality-Adjusted Life Year; SD – standard deviation

b) Use of proton beam therapy (PBT) to treat breast cancer (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Luo et al 2019	P1 Prospective case series Consecutive patients treated at 1 US centre between 2013 and 2015	n=42 Patients with non-metastatic breast cancer receiving adjuvant radiotherapy to the chest wall and regional nodes following mastectomy Patients with a history of prior radiation to the ipsilateral breast or chest wall were excluded Median age 46.5 years (range 21 to 86) % female not specified Tumour side: • Left: 86% • Right: 14%	PBT (3D conformal uniform scanning) Median dose 50 Gy RBE (range 45 to 61.2. Patients received a boost at the physician's discretion 76% had the internal mammary chain included in the radiation field 43% received neoadjuvant chemotherapy 62% had immediate reconstruction prior to radiotherapy Median follow-up: 35 months (range 1 to 55)	Primary Clinical effectiveness	Overall survival	Overall survival: 97.2% (median follow-up 35 months). 95%CI not reported	6	Direct	Patients had follow-up visits 1 to 2 months after radiotherapy and then approximately every 6 months. The median follow-up of 35 months may not be long enough to assess the impact of treatment on survival or chronic toxicities. This small study used data from 1 US centre from between 2013 and 2015. The applicability to current UK NHS clinical practice is unclear. The prospective design and inclusion of consecutive patients reduces the risk of selection bias. This study does not provide any information on the effectiveness of PBT compared to photon radiotherapy. The authors stated that there were no conflicts of interest.
				Primary Clinical effectiveness	Loco-regional disease free survival	3-year loco-regional disease free survival: 96.3% (median follow-up 35 months). 95%CI not reported			
				Primary Clinical effectiveness	Metastasis free survival	Metastasis free survival: 84.1% (median follow-up 35 months). 95%CI not reported Median time to development of distant metastatic disease: 11.7 months (range 0.6 to 14.6)			
				Safety	Adverse events Assessed using the Common Terminology Criteria for adverse Events, version 4.0[40]	**Acute toxicity (< 90 days after radiotherapy)** No grade 3 or 4 acute adverse events Grade 2 adverse events: • Dermatitis: 31 (74%) • Skin pain: 10 (24%) • Oesophagitis: 7 (17%) • Fatigue: 1 (2%) Grade 1 adverse events: • Dermatitis: 11 (26%) • Skin pain: 5 (12%) • Oesophagitis: 15 (36%) • Fatigue: 12 (29%) • Lymphedema: 8 (19%) 1 patient required a treatment break due to intolerance to dermatitis and skin pain. 1 patient did not receive boost			

[40] Grade 1 = '*mild*', Grade 2 = '*moderate*', Grade 3 = '*severe or medically significant but not immediately life-threatening*', Grade 4 = '*life-threatening consequences*', Grade 5 = '*death related to adverse event*' 'https://www.eortc.be/services/doc/ctc/ctcae_4.03_2010-06-14_quickreference_5x7.pdf

b) Use of proton beam therapy (PBT) to treat breast cancer (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						treatment due to concern of excessive skin toxicity **Chronic toxicity (> 90 days after radiotherapy)** No grade 2 or 4 acute adverse events Grade 3 adverse events: • Pneumonitis: 1 (2%) Grade 1 adverse events: • Dermatitis: 14 (33%) • Skin pain: 1 (2%) • Oesophagitis: 1 (2%) • Lymphedema: 12 (29%) • Hyperpigmentation: 17 (40%) • Telangiectasia: 1 (2%) No acute or chronic cardiac toxicities were reported			
				Safety	Reconstruction complications	7 of 26 patients (27%) who underwent immediate reconstruction followed by PBT developed reconstruction complications: • Capsular contractures: 6 • Implant infection: 1 5 patients had implants removed (reconstruction failure)			
Smith et al 2019	P1 Prospective case series Consecutive women with breast cancer treated at 1 US centre	n=51 Patients with breast cancer who had immediate implant based breast reconstruction and post-mastectomy	PBT (pencil beam scanning intensity modulated proton therapy) Median dose 50 Gy RBE (range 40.5 to 57.5) delivered in median 25 daily	Safety	Adverse events Assessed using the Common Terminology Criteria for adverse Events, version 4.0[40]	No grade 4 or 5 adverse events reported Grade 3 adverse events: • Radiation dermatitis: 2 (3.9%) Grade 2 adverse events: • Radiation dermatitis: 17 (33.3%) • Oesophagitis: 1 (2.0%) Grade 1 adverse events:	5	Direct	Patient characteristics and radiotherapy adverse events were collected prospectively. Complications relating to reconstruction were collected retrospectively through chart review. The authors also reported analysis comparing the risk of reconstruction complications in irradiated and non-irradiated breasts. This is out of scope for this review and is not reproduced.

b) Use of proton beam therapy (PBT) to treat breast cancer (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
	between 2015 and 2017	intensity modulated proton therapy Median age 49 (IQR 44 to 58) Female: 100% Tumour side: • Left: 69% • Right: 28% • Bilateral: 4%	fractions (range 15 to 25) Simultaneous integrated lymph node boosts were permitted. Chest wall boosts were not administered 84% received chemotherapy Median follow-up: 19 months (IQR 15 to 26)	 Safety	 Reconstruction complications	• Radiation dermatitis: 32 (62.7%) • Oesophagitis: 3 (5.9%) • Brachial plexopathy: 1 (2.0%) 20 (39.2%) had ≥1 complication Complications were reported separately for breasts irradiated with conventional fractionation or hypofractionation. No comparative analysis was reported Conventional fractionation (n=37) • Surgical site infection: 7 (18.9%) • Late infection: 1 (2.7%) • Seroma: 2 (5.4%) • Hematoma: 1 (2.7%) • Flap necrosis: 2 (5.4%) • Reconstruction failure: 3 (8.1%) Hypofractionation (n=14) • Surgical site infection: 7 (50%) • Late infection: 1 (7.1%) • Seroma: 2 (14.3%) • Contracture: 1 (7.1%) • Reconstruction failure: 5 (35.7%)			This small study used data from 1 US centre from between 2015 and 2017. The applicability to current UK NHS clinical practice is unclear. The prospective design and inclusion of consecutive patients reduces the risk of selection bias. This study does not provide any information on the effectiveness of PBT compared to photon radiotherapy. The authors stated that there were no conflicts of interest.
Liang et al 2018	S2 Retrospective case series Patients treated at 1 US centre between 2012 and 2016	n=23 Patients with breast cancer receiving adjuvant radiotherapy following mastectomy or lumpectomy Median age not reported	PBT (passive scattering technique) Dose 50 to 50.4 cobalt Gray equivalent Proportion of patients receiving chemotherapy not reported Median follow-up not reported	Safety	Skin toxicity Assessed using the Common Terminology Criteria for adverse Events, version 4.0[40]	10 patients (43%) had Grade 3 radiation dermatitis, including moist desquamation in areas other than skin folds and creases, bleeding by minor trauma or abrasion 23 patients (100%) had ≥ Grade 2 skin reactions including erythema or patchy moist desquamation confined to skin folds	3	Direct	The timeframe for the adverse events reported is not clear. The paper only reported skin toxicity. It is not clear if other adverse events were assessed. Limited information was provided on population and treatment characteristics. This very small study used data from 1 US centre from between 2012 and 2016. The applicability to current UK NHS clinical practice is unclear. The retrospective design introduces the possibility of selection bias in the completeness of the information reported.

b) Use of proton beam therapy (PBT) to treat breast cancer (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		% female not reported Tumour side not reported							This study does not provide any information on the effectiveness of PBT compared to photon radiotherapy. The authors stated that there were no conflicts of interest.
Ovalle et al 2018	S2 Retrospective case series Patients treated at 1 US centre between 2010 and 2015	n=43 Patients > 18 years old with stage 0-2 cancer, tumour ≤3 cm and ductal carcinoma in-situ or invasive adenocarcinoma. Included patients had ≥6 months follow-up Patients were excluded if they had >3 histologically-positive axillary nodes, multicentric carcinomas or definitive positive	PBT (accelerated partial breast irradiation; passively scattered) Prescribed dose 34 Gy RBE in 10 fractions, twice daily over 5 days Proportion of patients receiving chemotherapy not reported Median follow-up not reported	Safety	Adverse events Assessed by an author-developed scale assessing skin changes based on sub-categorisations of CTCAE v4.0[41] and an author-developed scale evaluating radiologic changes at 6 months[42]	**End of radiotherapy:** • 0 'no visual change': 64% • 1a 'faint erythema': 28% • 1b 'patchy erythema in ≤50% of the treated skin area': 8% Percentages for other categories only presented graphically (approximately 1% to 2%) **2 weeks follow-up:** • 0 'no visual change': 26% • 1b 'patchy erythema in ≤50% of the treated skin area': 60% Percentages for other categories only presented graphically (all < 10%) **6 weeks follow-up:** • 0 'no visual change': 7% • 1b 'patchy erythema in ≤50% of the treated skin area': 28% • 1c ''patchy erythema in >50% of the treated skin area': 33% • 1d 'dry desquamation limited to treated area': 16% Percentages for other categories only presented graphically (all < 10%)	4	Direct	Medical photographs were taken at the end of radiotherapy and at 2 weeks, 6 weeks and 6 months follow-up. A single physician reviewed all photographs and documented skin changes. An author-developed scale was used to assess medical photographs. Observed skin changes (erythema, desquamation, hyperpigmentation) were included in the scale. A second physician independently validated the skin toxicity score. An author-developed scale was used to assess 6-month follow-up mammograms and radiology reports. The number of reviewers was not stated. Results were presented graphically with exact percentages only reported for some adverse events. This small study used data from 1 US centre from between 2010 and 2015. The applicability to current UK NHS clinical practice is unclear. The retrospective design introduces the possibility of

[41] Erythema: 0 = '*no visual changes*', 1a = '*faint erythema*', 1b = '*patchy erythema in ≤50% of the treated skin area*', 1c = '*patchy erythema in >50% of the treated skin area*', 2a = '*confluent erythema over entire treated area*'. Desquamation: 1d = '*dry desquamation limited to treated area*', 3 = '*moist desquamation limited to treated area not in skin folds*'. Hyperpigmentation: 1a = '*mild hyperpigmentation limited to treated area*', 1b = '*moderate / severe hyperpigmentation limited to treated area*'

[42] Mammographic findings were used to create a 4-category scale evaluating the presence or absence of skin thickening, seroma/ hematoma, fat necrosis and retraction/ significant asymmetry. Skin thickening was assessed in comparison to the contralateral breast and measured in mm. Retraction/ significant asymmetry was graded as '*mild*', '*moderate*' or '*severe*'

b) Use of proton beam therapy (PBT) to treat breast cancer (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		surgical margins				**6 months follow-up** Skin changes: • 0 'no visual change': 57% • 1a 'mild hyperpigmentation limited to treated area': 33% • 1b 'moderate / severe hyperpigmentation limited to treated area': 5% Percentages for other categories only presented graphically (all < 10%) Radiologic changes: • Skin thickening: 40% (range 0mm to 5.5mm) • Seroma/ hematoma: 14% • Fat necrosis: 2% • Retraction/ significant asymmetry: 26% (9 of the 11 cases graded as mild)			selection bias in the completeness of the information reported. This study does not provide any information on the effectiveness of PBT compared to photon radiotherapy. The authors stated that there were no conflicts of interest
Verma et al 2017	S2 Retrospective case series Patients treated at 1 US centre between 2011 and 2016	n=91 Patients with breast cancer who received primary adjuvant radiotherapy to the breast or chest wall plus the comprehensive regional lymphatics (axilla, supraclavicular and internal mammary	PBT (3D uniform scanning 77%; pencil beam scanning 23%) Median dose to initial fields: 50.4Gy RBE (range 44.8 to 50.4) Patients received a boost at the discretion of the treating physician; median dose 10.0Gy RBE	Primary Clinical effectiveness	Mortality	6 patients (7%) had died at median follow-up 15.5 months	6	Direct	Toxicity was recorded weekly during treatment and every 6 months after treatment. Patients treated prior to 2016 received 3D uniform scanning. Patients treated in 2016 received pencil beam scanning when this technology became available at the centre. The median follow-up of 15. 5 months may not be long enough to assess the impact of treatment on mortality or disease failure. This small study used data from 1 US centre from between 2011 and 2016. The applicability to current UK NHS clinical practice is unclear. The retrospective design introduces the possibility of
				Primary Clinical effectiveness	Disease failure	12 patients (13%) had disease failure[43]: • Distant recurrence: 10 (11%) • Loco-regional recurrence: 4 (4%) 2 patients had both distant and loco-regional recurrence Median time to any failure: 8 months (range not reported)			
				Safety	Adverse events Assessed using the	No grade 4 or 5 adverse events reported Grade 3 adverse events: • Dermatitis: 5 (5%)			

[43] Loco-regional failure defined as imaging evidence of tumour in the ipsilateral breast or chest wall and/ or ipsilateral lymphatics. Other failures were categorised as distant

b) Use of proton beam therapy (PBT) to treat breast cancer (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		lymph nodes) following mastectomy or breast conserving surgery Patients were excluded if they were receiving re-irradiation, aggressive palliation for inoperable disease, partial breast irradiation, treatment to sites of distant metastatic disease or had isolated axillary recurrence. One patient who electively stopped treatment after 5 fractions was also excluded Median age 54 years (range 25-78) 98% female Tumour side: • Left: 62%	97% patients received chemotherapy 47% of patients receiving mastectomy had reconstruction prior to radiotherapy Median follow-up 15.5 months (range not reported)		Common Terminology Criteria for adverse Events, version 4.0[40]	• Breast/chest wall pain: 1 (1%) Grade 2 adverse events: • Dermatitis: 67 (72%) • Breast/chest wall pain: 27 (29%) • Oesophagitis: 30 (33%) • Fatigue: 5 (15%) Grade 1 adverse events: • Dermatitis: 21 (23%) • Breast/chest wall pain: 47 (50%) • Oesophagitis: 28 (31%) • Fatigue: 42 (46%) Median time to resolution of dermatitis 32 days (range not reported) Median time to resolution of pain 29 days (range not reported) 7 patients (8%) developed a skin infection requiring antibiotics 2 patients (2%) had uncomplicated rib fracture at 13 and 39 months follow-up 3 patients (3%) had clinically evident lymphoedema at last follow-up 2 patients did not complete the prescribed treatment; 1 discontinued due to grade 2 dermatitis and 1 patient declined a boost (reason not specified) **For patients receiving radiotherapy to the breast (n=27):** Grade 3 adverse events: • Dermatitis: 2 (7%) Grade 2 adverse events:			selection bias in the completeness of the information reported. This study does not provide any information on the effectiveness of PBT compared to photon radiotherapy. Two authors declared an association with a manufacturer. No other conflicts of interest were declared.

b) Use of proton beam therapy (PBT) to treat breast cancer (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		• Right: 36% • Bilateral: 2%				• Dermatitis: 15 (56%) • Breast pain: 14 (52%) • Oesophagitis: 8 (30%) • Fatigue: 2 (7%) Grade 1 adverse events: • Dermatitis: 10 (37%) • Breast pain: 11 (41%) • Oesophagitis: 9 (33%) • Fatigue: 14 (52%) **For patients receiving radiotherapy to the chest wall (n=66):** Grade 3 adverse events: • Dermatitis: 3 (5%) • Chest wall pain: 1 (2%) Grade 2 adverse events: • Dermatitis: 52 (79%) • Chest wall pain: 13 (20%) • Oesophagitis: 22 (33%) • Fatigue: 3 (5%) Grade 1 adverse events: • Dermatitis: 11 (16%) • Chest wall pain: 36 (55%) • Oesophagitis: 19 (29%) • Fatigue: 28 (42%)			
Bradley et al 2016	P1 Prospective case series Patients treated at 1 US centre between 2012 and 2014	n=10 Patients with stage II or III invasive adenocarcinoma breast cancer and indications for regional node irradiation who received	PBT (passive scattering technique) Dose 50.4 Gy RBE. An additional 10 to 16 Gy was delivered to selected patients	Safety	Adverse events Assessed using the Common Terminology Criteria for adverse Events, version 4.0[40]	There were no Grade 4 or 5 adverse events Grade 3 adverse events: • Dermatitis: 3 (30%) Grade 2 adverse events: • Dermatitis: 10 (100%) • Infection: 1 (10%) Other Grade 2 toxicities were reported for the whole population (n=18) with no	3	Direct	The study included 18 patients in total, of whom 8 received combined proton-photon radiotherapy. Results for these 8 patients are not reproduced. Information for adverse events where is it not clear if they relate to proton or proton-photon patients are indicated. Patient characteristics were reported for the whole study population (n=18), but were not separately reported for the 10 patients who received proton radiotherapy.

b) Use of proton beam therapy (PBT) to treat breast cancer (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		adjuvant radiotherapy after mastectomy or lumpectomy Median age not reported for proton radiotherapy patients. Age range for whole population 42 to 73 years 100% female Tumour side: • Left: 50% • Right: 50%	All but 1 of the total study population (n=18) received chemotherapy 33% of patients receiving mastectomy had reconstruction prior to radiotherapy Median follow-up not reported for proton radiotherapy patients. Follow-up range for whole population 2 to 31 months			indication of the number of proton radiotherapy patients affected. These were fatigue (n=6), oesophagitis (n=5), nausea (n=1), dyspnea (n=1)			Patients were assessed weekly during treatment, 4 weeks after radiotherapy and then at 6 month intervals. This very small study used data from 1 US centre from between 2012 and 2014. The applicability to current UK NHS clinical practice is unclear. The prospective design reduces the risk of selection bias. This study does not provide any information on the effectiveness of PBT compared to photon radiotherapy. The authors stated that there were no conflicts of interest.
Cuaron et al 2015	S2 Retrospective case series Patients treated at 1 US centre between 2013 and 2014	n=30 Patients with non-metastatic breast cancer receiving adjuvant radiotherapy to the breast/ chest wall and regional lymph nodes following mastectomy or lumpectomy	PBT (uniform scanning) Median dose 50.4 Gy RBE delivered in 5 weeks. Boosts were delivered at the physician's discretion 93% had the internal mammary nodes included in the radiation field	Primary Clinical effectiveness	Distant metastasis	1 patient (3%) developed distant metastasis 10 months after radiotherapy	4	Direct	Patients were assessed weekly during treatment, at 1 month after radiotherapy and at 3 to 6 month intervals afterwards. The median follow-up of 9.3 months may not be long enough to assess the impact of treatment on distant metastasis. This very small study used data from 1 US centre from between 2013 and 2014. The applicability to current UK NHS clinical practice is unclear. The retrospective design introduces the possibility of selection bias in the completeness of the information reported.
				Safety	Adverse events Assessed using the Common Terminology Criteria for adverse Events, version 4.0[40]	For patients with > 3 months follow-up (n=28): No Grade 3 or higher toxicities Grade 2 adverse events: • Dermatitis: 20 (71%) • Moist desquamation: 8 (29%) • Skin pain: 7 (25%) • Chest wall pain: 1 (4%) • Oesophagitis: 8 (29%) • Fatigue: 1 (4%) Grade 1 adverse events:			

b) Use of proton beam therapy (PBT) to treat breast cancer (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		Patients with a history of prior radiation were excluded Median age: 49 years (range 29-86) % female not reported Tumour side: • Left: 90% • Right: 10%	43% received neoadjuvant chemotherapy. 47% received adjuvant chemotherapy 50% received mastectomy plus reconstruction Median follow-up: 9.3 months (range 2.3 to 18.6)			• Dermatitis: 7 (25%) • Skin pain: 3 (11%) • Chest wall pain: 1 (4%) • Oesophagitis: 11 (39%) • Fatigue: 13 (46%) • Lymphedema: 8 (29%) No patients experienced rib fracture No patients experienced lung or cardiac toxicity No patients required a treatment break			This study does not provide any information on the effectiveness of PBT compared to photon radiotherapy. Three authors declared an association with a manufacturer. No other conflicts of interest were declared
				Safety	Reconstruction complications	2 of 15 patients (13%) experienced reconstructive complications (1 Grade 3 requiring removal and 1 Grade 1)			
Bush et al 2014	P1 Prospective case series Number of centres not stated Treatment years not stated	n=100 Patients with invasive nonlobular breast cancer (T1 or T2) with a maximal dimension of 3cm and no cancer in nearby lymph nodes Patients underwent partial mastectomy followed by radiotherapy	PBT (partial breast irradiation) Patients received 40 Gy in 10 fractions daily for 2 weeks 17% received chemotherapy Median follow-up 60 months (range not reported)	Primary Clinical effectiveness	Overall survival	95% (median follow-up 5 years). 95%CI not reported	4	Direct	The authors provided limited details for the outcomes reported. The grading system used to assess adverse events was not specified. However the language used (e.g. the description of grade 1 or 2 adverse effects as mild to moderate) is consistent with the National Cancer Institute Common Terminology Criteria for Adverse Events[44]. The median follow-up of 60 months may not be long enough to assess the impact of treatment on survival. The number of participating centres and year of treatment were not reported. The risk of bias due to different practices in different centres or over time is unknown. The applicability to current UK NHS clinical
				Primary Clinical effectiveness	Disease free survival	94% (median follow-up 5 years). 95%CI not reported			
				Primary Clinical effectiveness	Loco-regional survival	97% (95%CI 93 to 100) (median follow-up 5 years) No local failures with recurrence at the original tumour site			
				Primary Clinical effectiveness	Physician-rated cosmetic outcome Assessed by Harvard	The proportion reporting an '*excellent*' or '*good*' result was presented graphically. This was approximately 95% from baseline to 5 year follow-up The authors reported that no annual assessment was significantly different			

[44] https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

b) Use of proton beam therapy (PBT) to treat breast cancer (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		to the surgical bed Patients were excluded if they had extensive ductal carcinoma in situ Mean age 63 years (range 41 to 83) Patient gender was not reported Tumour side Left: 52% Right: 48%			Cosmesis Scale[34]	from baseline but did not report p values			practice is unclear. The prospective design reduces the risk of selection bias. This study does not provide any information on the effectiveness of PBT compared to photon radiotherapy. The authors stated that there were no conflicts of interest
				Primary Clinical effectiveness	Patient-reported cosmetic outcome Assessed by Harvard Cosmesis Scale[34]	The proportion reporting an '*excellent*' or '*good*' result was presented graphically. This was between approximately 90 and 95% from baseline to 5 year follow-up The authors reported that no annual assessment was significantly different from baseline but did not report p values			
				Safety	Adverse events Grading system not specified	**Acute adverse effects** (from radiotherapy initiation to 3 months after completion): No cases of ≥grade 3 acute skin reactions Grade 1-2 radiation dermatitis: 62 (62%) No other acute toxicities reported **Late adverse effects (not further defined):** Grade 1 telangiectasia: 7 (7%) Fat necrosis requiring drainage: 1 (1%) No cases of rib fracture, clinical pneumonitis or cardiac events All patients completed their assigned treatment without interruption			
Chang et al 2013	P1 Prospective case series	n=30 Patients ≥40 years old with breast cancer	PBT (proton beam accelerated partial breast irradiation)	Primary Clinical effectiveness	Overall survival	100% (median follow-up 59 months)	5	Direct	Patients were assessed 2 and 6 months after radiotherapy and then annually. Cosmetic outcomes were assessed by one radiation oncologist.

b) Use of proton beam therapy (PBT) to treat breast cancer (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
	Patients treated at 1 centre in Korea between 2007 and 2009	with tumours ≤3cm and pathologically negative axillary nodes who received adjuvant radiotherapy after breast conserving surgery Patients with intra-ductal carcinoma *in situ* were excluded Median age 48 years (range 40 to 69) % female not reported Tumour side: • Left: 53% • Right: 47%	Dose 30Gy RBE delivered once daily over 5 consecutive working days 57% had adjuvant chemotherapy Median follow-up 59 months (range 43 to 70)	Primary Clinical effectiveness	Loco-regional recurrence	There were no cases of local or regional recurrence (median follow-up 59 months)			The authors did not use a standardised framework to assess adverse events. The median follow-up of 60 months may not be long enough to assess the impact of treatment on survival and disease progression. This very small study used data from 1 Korean centre from between 2007 and 2009. The applicability to current UK NHS clinical practice is unclear. The prospective design reduces the risk of selection bias. This study does not provide any information on the effectiveness of PBT compared to photon radiotherapy. The study was funded by a research grant from the National Cancer Center, Korea. No conflicts of interest were declared
				Primary Clinical effectiveness	Distant metastasis	There were no cases of distant metastasis (median follow-up 59 months)			
				Primary Clinical effectiveness	Physician-rated cosmetic outcome Assessed qualitatively[45] and by the percentage breast retraction assessment[46]	**End of radiotherapy (n=30)** • Excellent: 5 (17%) • Good: 20 (67%) • Fair: 5 (17%) • Poor: 0 **At 2 months (n=30)** • Excellent: 5 (17%) • Good: 19 (63%) • Fair: 5 (17%) • Poor: 1 (3%) **At 6 months (n=30)** • Excellent: 5 (17%) • Good: 20 (67%) • Fair: 5 (17%) • Poor: 0 **At 1 year (n=30)** • Excellent: 5 (17%) • Good: 18 (60%) • Fair: 7 (23%) • Poor: 0 **At 2 years (n=27)** • Excellent: 5 (19%) • Good: 15 (56%)			

[45] Global cosmetic result, appearance of the surgical scar, breast size, breast shape, skin colour and location and shape of the areola and nipple were assessed on a 4-point scale where 0 = '*excellent result (no difference)*', 1 = '*good result (small difference)*', 2 = '*fair result (moderate difference)*', 3 = '*poor result (large difference)*'

[46] The treated breast was compared to the untreated breast by measuring the lateral and vertical displacement of the nipple

b) Use of proton beam therapy (PBT) to treat breast cancer (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						• Fair: 7 (26%) • Poor: 0 **At 3 years (n=23)** • Excellent: 4 (17%) • Good: 12 (52%) • Fair: 6 (26%) • Poor: 1 (4%) Mean percentage breast retraction increased significantly over the follow-up period from 10.5% at end of treatment to 15.3% at 3 years (p=0.002)			
				Primary Clinical effectiveness	Quality of life Assessed by the European Organization for Research and Treatment of Cancer (EORTC) 30 Quality of Life Questionnaire (QLQ) and the EORTC breast cancer specific questionnaire [47]	There were no significant differences in any functional scores on the EORTC 30 QLQ assessed before vs after the last day of radiotherapy (mean (SD)): • Global health status: 67.5 (22.8) vs 72.2 (18.1), p=0.378 • Physical functioning: 82.9 (12.7) vs 86.7 (10.5), p=0.215 • Role Functioning: 82.2 (17.5) vs 84.4 (18.5), p=0.635 • Emotional functioning: 69.2 (19.0) vs 76.4 (18.3), p=0.139 • Cognitive functioning: 85.6 (14.3) vs 86.1 (17.0), p=0.892 • Social functioning: 80.0 (23.3) vs 80.6 (23.6), p=0.927 There were no significant differences in any symptom scores on the EORTC 30 QLQ assessed before vs after the last day of radiotherapy (mean (SD)): • Fatigue: 30.7 (20.6) vs 27.4 (12.6), p=0.452			

[47] Patients completed functional and symptom scales before and after the last day of radiotherapy. Scores are out of 100 with higher functional scores and lower symptoms scores indicate better quality of life

b) Use of proton beam therapy (PBT) to treat breast cancer (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						• Nausea/ vomiting: 4.9 (10.1) vs 4.2 (11.7), p=0.795 • Pain: 27.2 (20.3) vs 18.9 (13.7), p=0.068 • Dyspnea: 11.1 (18.2) vs 7.8 (16.8), p=0.464 • Insomnia: 27.8 (24.9) vs 25.6 (20.9), p=0.709 • Appetite loss: 14.4 (20.9) vs 13.3 (16.6), p=0.820 • Constipation: 14.4 (18.9) vs 13.3 (22.5), p=0.837 • Diarrhoea: 6.7 (13.6) vs 8.9 (17.4), p=0.583 • Financial difficulties: 20.0 (20.7) vs 27.8 (27.8), p=0.224 There were no significant differences in any functional scores on the EORTC breast cancer specific questionnaire assessed before vs after the last day of radiotherapy (mean (SD)): • Body image: 76.7 (21.6) vs 74.4 (20.4), p=0.684 • Sexual function: 74.7 (26.6) vs 81.8 (18.1), p=0.183 • Future perspective: 46.7 (29.8) vs 47.8 (24.3), p=0.875 There were no significant differences in any symptom scores on the EORTC breast cancer specific questionnaire assessed before vs after the last day of radiotherapy (mean (SD)): • Systemic therapy side effects: 15.7 (11.1) vs 14.6 (10.7), p=0.695 • Breast symptoms: 23.3 (19.9) vs 18.9 (12.0), p=0.136 • Arm symptoms: 20.7 (21.4) vs 13.7 (13.9), p=0.136			

b) Use of proton beam therapy (PBT) to treat breast cancer (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
				Safety	Adverse events Assessed by a 4-point scale[48]	**End of radiotherapy (n=30)** No moderate or severe adverse events Mild adverse events • Breast pain: 8 (27%) • Breast oedema: 2 (7%) • Erythema / hyperpigmentation: 26 (87%) **At 2 months (n=30)** Severe adverse events: • Wet desquamation: 1 (3%) Moderate adverse events: • Breast oedema: 1 (3%) • Erythema / hyperpigmentation: 9 (30%) • Wet desquamation: 1 (3%) Mild adverse events • Breast pain: 11 (37%) • Breast oedema: 6 (20%) • Erythema / hyperpigmentation: 21 (70%) • Wet desquamation: 4 (13%) **At 6 months (n=30)** No severe adverse events Moderate adverse events: • Breast oedema: 1 (3%) • Erythema / hyperpigmentation: 4 (13%) • Induration: 1 (3%) Mild adverse events • Breast pain: 3 (10%)			

[48] 0 = '*none*', 1 = '*mild*', 2 = '*moderate*', 3 = '*severe*'

b) Use of proton beam therapy (PBT) to treat breast cancer (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						• Breast oedema: 4 (13%) • Erythema / hyperpigmentation: 24 (80%) • Wet desquamation: 1 (3%) • Induration: 4 (13%) **At 1 year (n=30)** No severe adverse events Moderate adverse events: • Erythema / hyperpigmentation: 4 (13%) • Induration: 2 (7%) Mild adverse events • Breast pain: 1 (3%) • Breast oedema: 2 (7%) • Erythema / hyperpigmentation: 20 (67%) • Induration: 7 (23%) **At 2 years (n=27)** No severe adverse events Moderate adverse events: • Erythema / hyperpigmentation: 2 (7%) • Induration: 1 (4%) Mild adverse events • Breast pain: 1 (4%) • Erythema / hyperpigmentation: 12 (44%) • Induration: 7 (26%) **At 3 years (n=23)** No severe adverse events Moderate adverse events:			

b) Use of proton beam therapy (PBT) to treat breast cancer (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						• Erythema / hyperpigmentation: 2 (9%) • Induration: 1 (4%) Mild adverse events • Breast pain: 1 (4%) • Erythema / hyperpigmentation: 12 (52%) • Induration: 6 (26%) 2 patients had rib fracture (1 at 6 months, 1 at 2 years)			
MacDonald et al 2013	P1 Prospective case series Patients treated at 1 US centre. Year of treatment not reported	n=12 Patients with invasive, non-metastatic breast cancer and unfavourable cardiac anatomy[49] who received adjuvant radiotherapy to the chest wall ± regional lymphatic radiation after mastectomy Median age 42 years (range 31 to 68) Tumour side: • Left: 92%	PBT (passive scattering technique) Dose 50.4 Gy RBE to the chest wall and 45 to 50.4 Gy to regional lymphatics 25% had internal mammary node involvement 42% had neoadjuvant chemotherapy. 58% had adjuvant chemotherapy 42% patients had reconstruction	Safety	Adverse events Assessed using the Common Terminology Criteria for adverse Events, version 4.0[40]	No Grade 4 or 5 adverse events **During radiotherapy** Grade 3 adverse events • Fatigue: 1 (8%) Grade 2 adverse events • Skin hyperpigmentation: 9 (75%) • Fatigue: 5 (42%) Grade 1 adverse events • Skin hyperpigmentation: 3 (25%) • Fatigue: 6 (50%) **At 4 weeks follow-up** Grade 1 adverse events • Skin hyperpigmentation: 8 (67%) • Fatigue: 1 (8%) **At 8 weeks follow-up** Grade 1 adverse events • Skin hyperpigmentation: 3 (25%) • Fatigue: 1 (8%) There were no radiation pneumonitis cases	4	Direct	Patients were assessed during treatment and at 4 and 8 weeks follow-up. It is unclear if all adverse events were reported. There were some discrepancies in the figures reported in different sections of the paper. This very small study used data from 1 US centre. Year of treatment was not reported. The applicability to current UK NHS clinical practice is unclear. The prospective design reduces the risk of selection bias. This study does not provide any information on the effectiveness of PBT compared to photon radiotherapy. The authors stated that there were no conflicts of interest.

[49] Defined as an estimated dose ≥5% of heart receiving 20Gy, the left anterior descending artery (LAD) receiving ≥20 Gy or both with conventional planning

b) Use of proton beam therapy (PBT) to treat breast cancer (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		• Right: 8%	prior to radiotherapy Median follow-up: 6 months (range 3.5 to 11.2)			The authors stated that analysis of cardiac toxicity was not performed for this paper			

CI – confidence intervals; Gy – Gray; IQR – interquartile range; PBT – proton beam therapy; RBE – relative biological effectiveness

8 Grade of Evidence Table

For abbreviations see list after each table

a) Use of proton beam therapy (PBT) vs. photon radiotherapy					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Overall survival	Chowdhary et al 2019	7	Direct	B	Overall survival was measured as time from diagnosis to time of death or last follow-up (Chowdhary et al 2019). In Chowdhary et al 2019 five-year overall survival was 91.9% for PBT patients (n=871) and 88.9% for photon radiotherapy patients (n=723,621) (95% CI not reported). Overall survival was not associated with PBT in multivariate analysis (HR 0.85 (95%CI 0.68 to 1.07), p=0.168). This analysis adjusted for factors including age, race, insurance status, comorbidity, treatment facility type, income, residence location, education, tumour side, stage, receptor status, chemotherapy, endocrine therapy, type of surgery and year of diagnosis. There was also no significant association between overall survival and PBT for subgroups of patients based on tumour side, quadrant location, type of surgery (mastectomy vs breast conserving), node positivity, N2-N3 positivity or the inclusion of lymph node irradiation. A high overall survival rate is important to clinicians, patients and their families. There was no difference for survival outcomes between different patient groups. These results need to be interpreted with caution because of the limitations of the study. This retrospective comparison used data from a national database of patients treated in the US between 2004 and 2014. The applicability to current UK NHS clinical practice is unclear. The retrospective design introduces the possibility of selection bias in the completeness of the information reported. The median follow-up of 62 months (range not reported) may not be long enough to assess the impact of treatment on overall survival.
Patient-reported cosmetic result	Teichman et al 2018	4	Direct	C	Patient-reported cosmetic result was assessed by the Harvard Cosmesis Scale. This single-item question rates cosmetic result as 4 = '*excellent*', 3 = '*good*', 2 = '*fair*' or 1 = '*poor*'. Teichman et al 2018 reported a statistically significantly better mean (standard deviation (SD)) result for PBT (n=69) vs photon radiotherapy (n=56) (3.40 (0.75) vs 2.44 (0.96), p<0.001). Data were collected at a median of 6.5 years post-diagnosis. Cosmetic outcome is an important outcome as this may impact quality of life. Cosmetic result was judged more positively by patients who were treated with PBT. These results need to be interpreted with caution because of the limitations of the study. This retrospective comparison used data from patients treated at 1 US centre between 2003 and 2012 who responded to a survey. The survey was sent to patients who were alive and disease-free 5 years or more after diagnosis. The response rate was 79%. The data may be subject to response bias as the people who responded to the survey may not reflect all patients treated. The proportion of non-responders who received PBT or photon radiotherapy was not specified. The applicability to current UK NHS clinical practice is unclear. The retrospective design introduces the possibility of selection bias in the completeness of the information reported. All but 2 of the 69 PBT patients

a) Use of proton beam therapy (PBT) vs. photon radiotherapy					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					received their treatment during a clinical trial. The photon radiotherapy patients received the conventional treatment at the time. This may have had a confounding effect on attitudes to the treatment received or perceptions of outcomes. The differences in treated volume (partial breast PBT vs whole breast photon radiotherapy) and delivery of radiotherapy (10 days vs 6 weeks) for the 2 groups may also have had a confounding effect.
Patient-reported treatment outcome	Teichman et al 2018	4	Direct	C	Patient-reported treatment outcome was assessed by the Breast Cancer Treatment Outcome Scale. This 22-item questionnaire evaluates functional and cosmetic outcome, reported as 4 subdomains: cosmetic, breast specific pain, functionality and oedema. Items are scored from 1 to 4 based on any difference between the treated and untreated breast where 1 = '*none*', 2 = '*slight*', 3 = '*moderate*' and 4 = '*large (major)*'. Teichman et al 2018 reported a statistically significantly better mean cosmetic score for PBT (n=72) vs photon radiotherapy (n=57) 1.45 vs 1.88, p<0.001). However the mean pain score was statistically significantly worse with PBT (1.42 vs 1.25, p<0.005). There was no significant difference in functionality (1.11 vs 1.17, p=0.311) or oedema (1.07 vs 1.12, p=0.526). The authors also created a weighted score based on the average of the 3 questions that patients thought were most important. This was statistically significantly better for PBT (1.84 vs 2.55, p<0.001). Standard deviation was not reported for this outcome. Data were collected at a median of 6.5 years post-diagnosis. Treatment outcome is an important outcome as it may impact quality of life. However, the clinical significance of this composite result is not clear as patients treated with PBT had statistically significant better cosmetic outcome but reported statistically significant worse pain. These results need to be interpreted with caution because of the limitations of the study. This retrospective comparison used data from patients treated at 1 US centre between 2003 and 2012 who responded to a survey. The survey was sent to patients who were alive and disease-free 5 years or more after diagnosis. The response rate was 79%. The data may be subject to response bias as the people who responded to the survey may not reflect all patients treated. The proportion of non-responders who received PBT or photon radiotherapy was not specified. The applicability to current UK NHS clinical practice is unclear. The retrospective design introduces the possibility of selection bias in the completeness of the information reported. All but 2 of the 69 PBT patients received their treatment during a clinical trial. The photon radiotherapy patients received the conventional treatment at the time. This may have had a confounding effect on attitudes to the treatment received or perceptions of outcomes. The differences in treated volume (partial breast PBT vs whole breast photon radiotherapy) and delivery of radiotherapy (10 days vs 6 weeks) for the 2 groups may also have had a confounding effect.
Body image	Teichman et al 2018	4	Direct	C	Body image was assessed by the Body Image Scale. This 10-item self-reported questionnaire assesses feelings about appearance and changes which may have resulted from a disease or treatment during the prior week. Each item is scored from 1 to 4 with higher scores indicating more dissatisfaction/ negative feelings, where 1 = '*not at all*', 2 = '*a little*', 3 = '*quite a bit*' and 4 = '*very much*'.

a) Use of proton beam therapy (PBT) vs. photon radiotherapy					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					Teichman et al 2018 reported a statistically significantly better mean (SD) result for PBT (n=72) vs photon radiotherapy (n=57) (12.04 (3.75) vs 13.91 (5.25), p<0.03). Data were collected at a median of 6.5 years post-diagnosis. Body image is an important outcome as this may impact quality of life. A statistical difference favouring PBT was reported. However the means reported suggest the difference may not be clinically significant. These results need to be interpreted with caution because of the limitations of the study. This retrospective comparison used data from patients treated at 1 US centre between 2003 and 2012 who responded to a survey. The survey was sent to patients who were alive and disease-free 5 years or more after diagnosis. The response rate was 79%. The data may be subject to response bias as the people who responded to the survey may not reflect all patients treated. The proportion of non-responders who received PBT or photon radiotherapy was not specified. The applicability to current UK NHS clinical practice is unclear. The retrospective design introduces the possibility of selection bias in the completeness of the information reported. All but 2 of the 69 proton radiotherapy patients received their treatment during a clinical trial. The photon radiotherapy patients received the conventional treatment at the time. This may have had a confounding effect on attitudes to the treatment received or perceptions of outcomes. The differences in treated volume (partial breast PBT vs whole breast photon radiotherapy) and delivery of radiotherapy (10 days vs 6 weeks) for the 2 groups may also have had a confounding effect.
General perspective	Teichman et al 2018	4	Direct	C	General perspective was assessed by 9 questions generated by the study authors which were scored on a 5-point scale from 1 = '*not at all*' to 5 = '*very much*'. Teichman et al 2018 reported statistically significantly better mean scores for PBT (n=72) vs photon radiotherapy patients (n=57) for the following questions: '*happy with treatment choice*' (4.92 vs 4.20, p<0.001), '*skin "felt different" since treatment*' (1.22 vs 1.95, p<0.001), '*changed attitude about sex*' (1.41 vs 1.94, p=0.012), '*breast cancer changed views of "myself and body"*' (1.57 vs 2.16, p=0.008) and '*worry about "disease coming back*"' (2.31 vs 3.27, p<0.001). The mean score was statistically significantly worse with PBT for the question: '*skin quality during treatment*' (1.50 vs 2.82, p<0.001). There was no significant difference for the following questions: '*changed how I live my daily life*' (2.00 vs 2.30, p=0.197), '*role of spirituality/ religion*' (4.35 vs 4.00, p=0.116) and '*upper arms/ mobility issues*' (1.19 vs 1.30, p=0.348). Standard deviation was not reported for this outcome. Data were collected at a median of 6.5 years post-diagnosis. General perspective covers a range of areas that could impact quality of life. Some of the results favoured PBT. However, these did not translate to a difference between the groups for questions about change in daily life or upper arm/mobility issues. These results need to be interpreted with caution because of the limitations of the study. This retrospective comparison used data from patients treated at 1 US centre between 2003 and 2012 who responded to a survey. The survey was sent to patients who were alive and disease-free 5 years or more after diagnosis. The response rate was 79%. The data may be subject to response bias as the people who responded to the survey may not reflect all patients treated. The proportion

a) Use of proton beam therapy (PBT) vs. photon radiotherapy					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					of non-responders who received PBT or photon radiotherapy was not specified. The applicability to current UK NHS clinical practice is unclear. The retrospective design introduces the possibility of selection bias in the completeness of the information reported. All but 2 of the 69 PBT patients received their treatment during a clinical trial. The photon radiotherapy patients received the conventional treatment at the time. This may have had a confounding effect on attitudes to the treatment received or perceptions of outcomes. The differences in treated volume (partial breast PBT vs whole breast photon radiotherapy) and delivery of radiotherapy (10 days vs 6 weeks) for the 2 groups may also have had a confounding effect.
Fatigue	Teichman et al 2018	4	Direct	C	Fatigue was assessed by the Brief Fatigue Inventory. This 9-item self-reported questionnaire is scored on a scale of 0 '*no fatigue*' to 10 '*as bad as you can imagine*'. An average total score was calculated for 8 of the 9 items. The 9th item (see below) was reported separately. Teichman et al 2018 reported a statistically significantly better mean (SD) result for PBT (n=72) vs photon radiotherapy patients (n=57) (15.3 (17.11) vs 27.25 (22.26), p<0.002). The authors also created a weighted score based on the average of the 3 questions that patients thought were most important. There was no significant difference between the groups (1.84 vs 2.55, p<0.001). Standard deviation was not reported for this outcome. The proportion of patients responding '*yes*' to the question '*have you felt unusually tired or fatigued in the last week*' was 25% for PBT (n=71) and 63% (n=51) for photon radiotherapy. No significance test was reported. Data were collected at a median of 6.5 years post-diagnosis. Fatigue is an important outcome as this may impact quality of life. A statistical difference favouring PBT was reported. However there was no difference for the weighted mean, focusing on what patients thought was most important. The significance of the difference in recent tiredness is not clear. These results need to be interpreted with caution because of the limitations of the study. This retrospective comparison used data from patients treated at 1 US centre between 2003 and 2012 who responded to a survey. The survey was sent to patients who were alive and disease-free 5 years or more after diagnosis. The response rate was 79%. The data may be subject to response bias as the people who responded to the survey may not reflect all patients treated. The proportion of non-responders who received PBT or photon radiotherapy was not specified. The applicability to current UK NHS clinical practice is unclear. The retrospective design introduces the possibility of selection bias in the completeness of the information reported. All but 2 of the 69 PBT patients received their treatment during a clinical trial. The photon radiotherapy patients received the conventional treatment at the time. This may have had a confounding effect on attitudes to the treatment received or perceptions of outcomes. The differences in treated volume (partial breast PBT vs whole breast photon radiotherapy) and delivery of radiotherapy (10 days vs 6 weeks) for the 2 groups may also have had a confounding effect.
Skin toxicity	DeCesaris et al 2019	7	Direct	B	Skin toxicity was assessed by the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. On this scale Grade 1 = '*mild*', Grade 2 = '*moderate*', Grade 3 = '*severe or medically significant but not immediately life-threatening*', Grade 4 = '*life-threatening consequences*' and

a) Use of proton beam therapy (PBT) vs. photon radiotherapy					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					Grade 5 = '*death related to adverse event*'[50]. Two specific skin toxicity adverse events were assessed by DeCesaris et al 2019: radiation dermatitis[51] and skin hyperpigmentation[52]. *Radiation dermatitis*: There were no Grade 4 or 5 cases. There was no significant difference in Grade 3 radiation dermatitis between PBT (n=39) and photon (n=47) radiotherapy (5.1% vs 4.3%, p=0.848). Acute radiation dermatitis ≥ Grade 2 was statistically significantly higher with PBT (69.2% vs 29.8%, p<0.01). The highest recorded grade of radiation dermatitis was also statistically significantly higher with PBT (p=0.002). *Skin hyperpigmentation*: There was no significant difference between PBT and photon radiotherapy in skin hyperpigmentation ≥ Grade 2 (7.7% vs 12.8%, p=0.502). There was also no significant difference in the highest recorded grade of skin hyperpigmentation (p=0.413). At first clinical follow-up (within 8 weeks of treatment completion) there was no difference in sustained skin reactions between PBT (n=29) and photon radiotherapy (n=41) (Grade 1 radiation dermatitis 17.2% vs 19.5%, p=0.810; Grade 1 skin hyperpigmentation 65.5% vs 61.0%, p=0.698). Skin toxicity adverse events are important outcomes as they may affect function and quality of life. There was more Grade 2 (moderate) acute radiation dermatitis with PBT but there was no significant difference at clinical follow-up. There was no difference between the treatment groups in skin hyperpigmentation. These results need to be interpreted with caution because of the limitations of the study. This retrospective comparison used data from patients treated at 1 US centre between 2015 and 2017. The applicability to current UK NHS clinical practice is unclear. The retrospective design introduces the possibility of selection bias in the completeness of the information reported. Only patients with weekly on-treatment visit documentation of acute treatment related toxicities were included. Data from first clinical follow-up were only available for 74% and 87% of PBT and photon patients respectively. Toxicities were primarily scored by the same physician for both treatments.
Incremental cost effectiveness ratio (ICER)	Mailhot Vega et al 2017	5	Direct	C	ICER[53] was reported for a range of different scenarios based on the woman's age and mean radiotherapy heart dose. A treatment strategy was assessed for cost effectiveness against a willingness to pay threshold of either $50,000/ quality-adjusted life year (QALY) (£40,102) or $100,000/ QALY (£80,205).

[50] https://www.eortc.be/services/doc/ctc/ctcae_4.03_2010-06-14_quickreference_5x7.pdf

[51] Radiation dermatitis was scored as grade 1 = '*faint erythema or dry desquamation*'; grade 2 = '*moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate oedema*'; grade 3 = '*moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion*'; grade 4 = '*life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated*'; grade 5 = '*death*'

[52] Skin hyperpigmentation was scored as grade 1 = '*hyperpigmentation covering <10% body service area; no psychological impact*'; grade 2 = '*hyperpigmentation covering >10% body service area; psychological impact*'. Grades 3 to 5 not applicable for this adverse event

[53] Mailhot Vega et al (2017) described the ICER as the ratio of the difference in costs between PBT and photon radiotherapy and the difference in effectiveness between PBT and photon radiotherapy

a) Use of proton beam therapy (PBT) vs. photon radiotherapy					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					In Mailhot Vega et al 2017, PBT was not cost effective for women without cardiac risk factors compared to photon radiotherapy at a threshold of $50,000/ QALY. This remained the case following sensitivity analysis. • At a threshold of $50,000/QALY PBT was cost effective compared to photon radiotherapy for women with 1 or more cardiac risk factors for 50 year old women receiving a mean heart dose of 9Gy and 60 year old women receiving a mean heart dose of 10Gy • At a threshold of $100,000/ QALY there were scenarios (based on woman's age and mean radiotherapy heart dose) where PBT was cost effective compared to photon radiotherapy for both women with and without cardiac risk factors. This study indicates that for some women with 1 or more cardiac risk factors, there may be patient selection factors (based on age and mean heart dose) for which PBT would potentially be more cost effective than photon radiotherapy at a willingness to pay threshold of $50,000. These results are not generalisable to a UK NHS context because the willingness to pay thresholds used were higher than the threshold that is commonly used by NICE (£20,000 to £30,000). Additional concerns include the use of a societal perspective for 2012 US dollars. This overestimates the duration of the effect and underestimates the ICER value. The study also used of a lifetime horizon ending at patient death or age 100 years which may make the intervention appear more cost effective than if a lower, more realistic, age cut-off had been used. Conversions from US dollars to UK pounds were calculated in September 2019.

CI - Confidence Interval; CTCAE – Criteria for Adverse Events; Gy – Gray; HR – Hazard Ratio; ICER - Incremental Cost Effectiveness Ratio; PBT – Proton Beam Therapy; QALY - Quality-Adjusted Life Year; SD – Standard Deviation

b) Use of proton beam therapy (PBT) to treat breast cancer (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Overall survival	Luo et al 2019	6	Direct	B	Overall survival was measured from end of treatment to time of death or last follow-up. In Luo et al 2019 (n=42) overall survival was 97.2% (95%CI not reported) at a median follow-up of 35 months (range 1 to 55). The high overall survival rate of 97% will be of importance to clinicians, patients and their families. The results of this small prospective case series should be treated with caution. It does not provide any information on the effectiveness of PBT compared to photon radiotherapy. The study was conducted at 1 US centre between 2013 and 2015. The applicability to current UK NHS clinical practice is unclear. The median follow-up of 35 months may not be long enough to assess the impact of treatment on overall survival.
	Bush et al 2014	4	Direct		
	Chang et al 2013	5	Direct		
Mortality	Verma et al 2017	6	Direct	C	Mortality records the number of patients that had died at last follow-up.

b) Use of proton beam therapy (PBT) to treat breast cancer (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					In Verma et al 2017 (n=91) 6 patients (7%) had died at a median follow-up of 15.5 months (range not reported). A low mortality rate of 7% will be of importance to clinicians, patients and their families. The results of this small retrospective case series should be treated with caution. It does not provide any information on the effectiveness of PBT compared to photon radiotherapy. The retrospective design introduces the possibility of selection bias in the completeness of the information reported. The study was conducted at 1 US centre between 2011 and 2016. The applicability to current UK NHS clinical practice is unclear. The median follow-up of 15.5 months may not be long enough to assess the impact of treatment on mortality.
Disease free survival	Bush et al 2014	4	Direct	C	Disease free survival was not defined by Bush et al (2014) but is generally the time period without any signs or symptoms of disease (local, regional or distant), measured from the end of treatment. In Bush et al 2014 (n=100) disease-free survival was 94% (95%CI not reported) with a median follow-up of 5 years (range not reported). Disease-free survival assesses the success of treatment and is important to clinicians, patients and their families. 94% of patients were disease free at 5 years follow-up. The results of this small prospective case series should be treated with caution. It does not provide any information on the effectiveness of PBT compared to photon radiotherapy. The study was conducted in the US but the number of participating centres and year of treatment were not reported. The applicability to current UK NHS clinical practice is unclear. The median follow-up of 5 years may not be long enough to assess the impact of treatment on disease free survival.
Disease failure	Verma et al 2017	6	Direct	C	Disease failure included loco-regional recurrence and distant disease. Loco-regional failure was defined as imaging evidence of tumour in the ipsilateral breast or chest wall and/ or ipsilateral lymphatics. Others failures were categorised as distant. In Verma et al 2017 (n=91) 12 patients (13%) had disease failure at a median follow-up of 15.5 months (range not reported). 10 patients (11%) had distant recurrence and 4 patients (4%) had loco-regional recurrence (2 patients had both distant and loco-regional recurrence). Median time to any disease failure was 8 months (range not reported). Disease failure assesses the success of treatment and is important to clinicians, patients and their families. Most of the disease failures observed were distant disease. The results of this small retrospective case series should be treated with caution. It does not provide any information on the effectiveness of PBT compared to photon radiotherapy. The retrospective design introduces the possibility of selection bias in the completeness of the information reported. The study was conducted at 1 US centre between 2011 and 2016. The applicability to current UK NHS clinical practice is unclear. The median follow-up of 15.5 months may not be long enough to assess disease failure.

b) Use of proton beam therapy (PBT) to treat breast cancer (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Loco-regional disease free survival	Luo et al 2019	6	Direct	B	Loco-regional disease free survival was measured from end of treatment to time of loco-regional recurrence or last follow-up (Luo et al 2019). In Luo et al 2019 (n=42) loco-regional disease free survival was 96.3% (95%CI not reported) at a median follow-up of 35 months (range 1 to 55). Loco-regional disease free survival assesses the success of treatment and is important to clinicians, patients and their families. 96% of patients had not developed loco-regional recurrence at 35 months follow-up. The results of this small prospective case series should be treated with caution. It does not provide any information on the effectiveness of PBT compared to photon radiotherapy. The study was conducted at 1 US centre between 2013 and 2015. The applicability to current UK NHS clinical practice is unclear. The median follow-up of 35 months may not be long enough to assess the impact of treatment on loco-regional disease free survival.
	Bush et al 2014	4	Direct		
Loco-regional recurrence	Chang et al 2013	5	Direct	C	Loco-regional recurrence was measured from end of treatment to time of loco-regional recurrence or last follow-up. In Chang et al 2013 (n=30) there were no cases of loco-regional recurrence at a median follow-up of 59 months (range 43 to 70). Loco-regional recurrence assesses the success of treatment and is important to clinicians, patients and their families. No patients had developed loco-regional recurrence at 59 months follow-up. The results of this very small prospective case series should be treated with caution. It does not provide any information on the effectiveness of PBT compared to photon radiotherapy. The study was conducted at 1 centre in Korea between 2007 and 2009. The applicability to current UK NHS clinical practice is unclear. The median follow-up of 59 months may not be long enough to assess the impact of treatment on loco-regional recurrence.
Metastasis free survival	Luo et al 2019	6	Direct	C	Metastasis free survival was measured from end of treatment to time of metastasis or last follow-up (Luo et al 2019). In Luo et al 2019 (n=42) metastasis free survival was 84.1% (95%CI not reported) at a median follow-up of 35 months (range 1 to 55). Metastatic disease indicates a progression of disease and is important to clinicians, patients and their families. 84% had not developed metastasis at 35 months follow-up. The results of this small (n=42) prospective case series should be treated with caution. It does not provide any information on the effectiveness of PBT compared to photon radiotherapy. The study was conducted at 1 US centre between 2013 and 2015. The applicability to current UK NHS clinical practice is unclear. The median follow-up of 35 months may not be long enough to assess the impact of treatment on metastasis free survival.

b) Use of proton beam therapy (PBT) to treat breast cancer (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Distant metastasis	Cuaron et al 2015	4	Direct	B	Distant metastasis was measured from end of treatment to time of distant metastasis or last follow-up. In Chang et al 2013 (n=30) there were no cases of distant metastasis at a median follow-up of 59 months (range 43 to 70). Distant metastasis indicated a progression of disease and is important to clinicians, patients and their families. No patients had developed distant metastasis at 59 months follow-up. The results of this very small prospective case series should be treated with caution. It does not provide any information on the effectiveness of PBT compared to photon radiotherapy. The study was conducted at 1 centre in Korea between 2007 and 2009. The applicability to current UK NHS clinical practice is unclear. The median follow-up of 59 months may not be long enough to assess the impact of treatment on distant metastasis.
	Chang et al 2013	5	Direct		
Physician-rated cosmetic outcome	Bush et al 2014	4	Direct	B	Physician-rated cosmetic outcome assessed global cosmetic result, appearance of the surgical scar, breast size, breast shape, skin colour and location and shape of the areola and nipple. This was assessed on a 4-point scale where 0 = '*excellent result (no difference)*', 1 = '*good result (small difference)*', 2 = '*fair result (moderate difference)*', 3 = '*poor result (large difference)*'. Percentage of breast retraction was also assessed by comparing the lateral and vertical displacement of the nipple in the treated breast compared to the untreated breast. In Chang et al 2013 the proportion of outcomes rated '*excellent*' or '*good*' were: 84% at the end of radiotherapy (n=30), 80% at 2 months (n=80), 84% at 6 months (n=30), 77% at 1 year (n=30), 75% at 2 years (n=27) and 69% at 3 years (n=23). Mean percentage breast retraction increased statistically significantly over time from 10.5% at the end of treatment to 15.3% at 3 years (p=0.002). Cosmetic outcome is important as it may impact quality of life. Physician-rated cosmetic outcome was generally positive, but worsened over time. The results of this very small prospective case series should be treated with caution. It does not provide any information on the effectiveness of PBT compared to photon radiotherapy. The study was conducted at 1 centre in Korea between 2007 and 2009. The applicability to current UK NHS clinical practice is unclear. Cosmetic outcome was assessed by 1 radiation oncologist.
	Chang et al 2013	5	Direct		
Patient-reported cosmetic outcome	Bush et al 2014	4	Direct	C	Patient-reported cosmetic result for the treated breast was assessed by the Harvard Cosmesis Scale. This single-item question rates cosmetic result as 4 = '*excellent*', 3 = '*good*', 2 = '*fair*' or 1 = '*poor*'. The proportion of patients who rated the cosmetic outcome as '*excellent*' or '*good*' was reported by Bush et al (2014). In Bush et al 2014 (n=100) the proportion of patients reporting an '*excellent*' or '*good*' result was between approximately 90% and 95% at baseline and at median 5 year follow-up (range not reported). The authors reported that no annual assessment was significantly different from baseline (figures not reported).

b) Use of proton beam therapy (PBT) to treat breast cancer (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					Cosmetic outcome is an important outcome as this may impact on quality of life. Patient-rated cosmetic outcome was generally positive. The results of this small prospective case series should be treated with caution. It does not provide any information on the effectiveness of PBT compared to photon radiotherapy. The study was conducted in the US but the number of participating centres and year of treatment were not reported. The applicability to current UK NHS clinical practice is unclear. Precise figures for this outcome were not available as the results were only presented graphically.
Quality of life	Chang et al 2013	5	Direct	C	Quality of life was assessed by the European Organization for Research and Treatment of Cancer 30 Quality of Life Questionnaire (EORTC QLQ-C30) and the EORTC breast cancer specific questionnaire (EORTC QLQ-BR23). These are scored out of 100 with higher functional scores and lower symptoms scores indicating better quality of life. The EORTC QLQ-C30 includes 6 functional subscales (global health status, physical, role, emotional cognitive and social functioning) and 9 symptom subscales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties). The EORTC QLQ-BR23 includes 3 functional subscales (body image, sexual function and future perspective) and 3 symptom subscales (systemic therapy side effects, breast symptoms and arm symptoms). In Chang et al 2013 (n=30) there were no significant differences before treatment and after the last day of radiotherapy for any of the 6 functional subscales or 9 symptom subscales on the general quality of life questionnaire. There were also no significant differences for any of the 3 functional subscales or 3 symptom subscales on the breast cancer specific quality of life questionnaire. Impact of treatment on quality of life is important to clinicians, patients and their families. There was no difference in quality of life before and after treatment. The results of this very small prospective case series should be treated with caution. It does not provide any information on the effectiveness of PBT compared to photon radiotherapy. The study was conducted at 1 centre in Korea between 2007 and 2009. The applicability to current UK NHS clinical practice is unclear.
Adverse events	Luo et al 2019	6	Direct	B	In the two highest scoring studies (Luo et al 2019, Verma et al 2017) adverse events were assessed by the CTCAE Version 4.0. On this scale Grade 1 = '*mild*', Grade 2 = '*moderate*', Grade 3 = '*severe or medically significant but not immediately life-threatening*', Grade 4 = '*life-threatening consequences*' and Grade 5 = '*death related to adverse event*'[50]. In Luo et al 2019 (n=42) there were no acute adverse events (<90 days after radiotherapy) of Grade 3 or higher. Grade 2 (moderate) acute adverse events included dermatitis (74%), skin pain (24%), oesophagitis (17%) and fatigue (2%). There was 1 (2%) Grade 3 (severe) chronic adverse event (pneumonitis) >90 days after radiotherapy. There were no Grade 2 chronic adverse events. The authors reported that no acute or chronic cardiac toxicities were reported. Median follow-up was 35 months (range 1 to 55).
	Smith et al 2019	5	Direct		
	Ovalle et al 2018	4	Direct		
	Verma et al 2017	6	Direct		
	Bradley et al 2016	3	Direct		
	Cuaron et al 2015	4	Direct		
	Bush et al 2014	4	Direct		
	Chang et al 2013	5	Direct		

b) Use of proton beam therapy (PBT) to treat breast cancer (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
	MacDonald et al 2013	4	Direct		In Verma et al 2017 (n=91) there were no Grade 4 or 5 adverse events. Grade 3 (severe) adverse events included dermatitis (5%) and breast/ chest wall pain (1%). Grade 2 (moderate) adverse events included dermatitis (72%), breast/ chest wall pain (29%), oesophagitis (33%) and fatigue (15%). In addition, 8% developed a skin infection, 2% had uncomplicated rib fracture, and 3% had clinically evident lymphoedema. Adverse events were also separately reported for patients who received radiotherapy to the breast (n=27) and chest wall (n=66). The only Grade 3 adverse event for breast radiotherapy patients was dermatitis (7%). Grade 3 adverse events for chest wall radiotherapy patients included dermatitis (5%) and pain (2%). Grade 2 adverse events for breast radiotherapy patients included dermatitis (56%), pain (52%), oesophagitis (30%) and fatigue (7%). Grade 2 adverse events for chest wall radiotherapy patients included dermatitis (79%), pain (20%), oesophagitis (33%) and fatigue (5%). Median follow-up 15.5 months (range not reported). Adverse events are important outcomes as they may impact on quality of life. A small proportion of patients had Grade 3 (severe) adverse events in both studies. The proportion of patients experiencing Grade 2 (moderate) adverse events was higher, particularly for dermatitis. The results of these two small case series should be treated with caution. They do not provide any information on the effectiveness of PBT compared to photon radiotherapy. The retrospective design of Verma et al 2017 introduces the possibility of selection bias in the completeness of the information reported. Both studies were conducted in the US, Luo et al between 2013 and 2015 and Verma et al between 2011 and 2015. The applicability to current UK NHS clinical practice is unclear. The median follow-up of 35 and 15.5 months respectively may not be long enough to assess the impact of longer term toxicities.
Skin toxicity	Liang et al 2018	3	Direct	C	Skin toxicity was assessed by the CTCAE Version 4.0. On this scale Grade 1 = '*mild*', Grade 2 = '*moderate*', Grade 3 = '*severe or medically significant but not immediately life-threatening*', Grade 4 = '*life-threatening consequences*' and Grade 5 = '*death related to adverse event*'[50]. In Liang et al 2018 (n=23) 10 patients (43%) had Grade 3 radiation dermatitis. 23 patients (100%) had ≥ Grade 2 skin reactions including erythema or patchy moist desquamation confined to skin folds. Median follow-up was not reported. Skin toxicity adverse events are important outcomes as they may impact on quality of life. All patients had Grade 2 (moderate) toxicities and 43% had Grade 3 (severe) toxicities. The results of this very small retrospective case series should be treated with caution. It does not provide any information on the effectiveness of PBT compared to photon radiotherapy. The retrospective design introduces the possibility of selection bias in the completeness of the information reported. The study was conducted at 1 US centre between 2012 and 2016. The applicability to current UK NHS clinical practice is unclear.
Reconstruction complications	Luo et al 2019	6	Direct	B	Reconstruction complications were reported for patients who received PBT after a mastectomy with immediate reconstruction.
	Smith et al 2019	5	Direct		

b) Use of proton beam therapy (PBT) to treat breast cancer (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					In Luo et al 2019 (n=42) 7 of 26 patients (27%) who underwent PBT after immediate reconstruction developed complications. This included 6 capsular contractures and 1 implant infection. Implants were removed in 5 patients. Reconstruction complications are important as they could lead to further surgery and impact quality of life. 27% of patients had complications and 19% had an implant removed. The results of this small prospective case series should be treated with caution. It does not provide any information on the effectiveness of PBT compared to photon radiotherapy. The study was conducted at 1 US centre between 2013 and 2015. The applicability to current UK NHS clinical practice is unclear.

CI – Confidence Interval; CTCAE - Common Terminology Criteria for Adverse Events; EORTC QLQ-C30 - European Organization for Research and Treatment of Cancer 30 Quality of Life Questionnaire; EORTC QLQ-BR23- European Organization for Research and Treatment of Cancer Quality of Life Questionnaire breast cancer specific questionnaire; PBT – Proton Beam Therapy

9 Literature Search Terms

P –Population and Indication Describe the relevant population and indication provided previously including if necessary disease severity or duration, previous treatment, new or recurrent symptoms, any specific co-morbidities and other population factors (for example, age range). Add details of any subgroups or stratifications for which separate evidence may be required.	People of all ages undergoing adjuvant radiotherapy for breast cancer Subgroups of interest: a) People receiving radiotherapy to breast / chest wall and internal mammary nodes b) People with pectus excavatum
I – Intervention Describe the intervention details provided previously including if necessary details of treatment, mode of delivery, size/frequency/duration of dose, position of intervention in treatment pathway (e.g. first/second line/salvage) and any background / concomitant medication	Proton beam therapy Alternative terms (radiotherapy with protons, protons, particle therapy)
C – Comparators What is/are the main alternative/s to compare with the intervention being considered? Describe the comparator details provided previously including if necessary details of treatment, mode of delivery, size/frequency/duration of dose, position of intervention in treatment pathway (e.g. first/second line/salvage) and any background / concomitant medication	(Photon) radiotherapy [Types of radiotherapy that are relevant would include but are not limited to a) Deep inspiration breath hold radiotherapy b) Volumetric arc radiotherapy c) IMRT (Intensity Modulated Radiotherapy) d) Whole breast radiotherapy e) Chest wall radiotherapy f) Tomotherapy] (Partial breast radiotherapy is excluded as a comparator in this review as evidence for partial breast radiotherapy is addressed in a separate previous review)

O – Outcomes
Outcomes should be patient focussed and relate to those detailed in the PPP and the Research Questions covering clinical effectiveness, safety and cost effectiveness as required.
Examples will be topic specific but might include intermediate or short-term outcomes; mortality; morbidity; quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.
	Critical to decision-making:
	
	• Late side effects (after 6 weeks)
	  • Cardiac toxicity (long-term incidence of ischaemic heart disease/ myocardial infarction/ ischaemic heart death)
	  • Lung radiation toxicity
	  • Radiation induced second malignancy
	• Local control (may be presented as local recurrence or relapse rates)
	• Disease free survival
	• Progression free survival
	• Overall survival
	• Quality of life
	
	Important to decision-making:
	• Acute toxicity
	  • Skin toxicity
	  • Oesophagitis
	• Morbidity
	• Late radiation effects

	• Pneumonitis • Cosmetic effects (or cosmetic side effects) • Telangiectasia • Breast shrinkage and firmness • Regional recurrence • Other toxicity or radiation toxicity outcomes • Cost effectiveness outcomes
Inclusion criteria	
Study design	Published, peer reviewed systematic reviews, randomised controlled trials, controlled clinical trials, comparative cohort studies. If no higher level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	All ages
Date limits	2009-2019
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters and editorials
Study design	Case reports, resource utilisation studies, dosimetric planning studies

10 Search Strategy

We searched Medline, Embase and Cochrane Library limiting the search to papers published in English from 1st January 2009 to 1st August 2019. We excluded conference abstracts, commentaries, letters, editorials and case reports.

Search date: 1st August 2019
Embase search:

1	Proton Therapy/
2	((proton* or particle) adj3 (therap* or radiotherap* or treatment)).ti,ab.
3	(proton* or particle*).ti.
4	1 or 2 or 3
5	exp Breast Cancer/
6	(breast* adj5 (cancer? or carcinoma? or malignan* or tumo?r? or neoplas*)).ti,ab.
7	breast.ti.
8	((breast or chest wall) adj5 (irradiat* or radiat* or radiotherap*)).ti,ab.
9	5 or 6 or 7 or 8
10	4 and 9
11	(conference* or editorial or letter or note or "review").pt. or case report.ti,ab.
12	10 not 11
13	limit 10 to "reviews (maximizes specificity)"
14	12 or 13

15 (exp animals/ or nonhuman/) not human/
16 14 not 15
17 limit 16 to (english language and yr="2009 -Current")

11 Evidence Selection

- Total number of publications reviewed: 68
- Total number of publications considered potentially relevant: 23
- Total number of publications selected for inclusion in this briefing: 14

References from the PWG supplied in the PPP		Paper selection decision and rationale if excluded
1	Galland-Girodet, S., Pashtan, I., MacDonald, S., Ancukiewicz, M., Hirsch, A., Kachnic, L., Specht, M., Gadd, M., Smith, B., Powell, S., Recht, A. and Taghian, A. (2014). Long-term Cosmetic Outcomes and Toxicities of Proton Beam Therapy Compared With Photon-Based 3-Dimensional Conformal Accelerated Partial-Breast Irradiation: A Phase 1 Trial. International	Not included in this review. This study was included in the previous review of breast cancer for PBT. The PICO states that studies with partial breast photon radiotherapy as a comparator are excluded in this review as evidence for partial breast radiotherapy is addressed in a separate previous review.
2	Verma, V., Iftekaruddin, Z., Badar, N., Hartsell, W., Han-Chih Chang, J., Gondi, V., Pankuch, M., Gao, M., Schmidt, S., Kaplan, D. and McGee, L. (2017). Proton beam radiotherapy as part of comprehensive regional nodal irradiation for locally advanced breast cancer. Radiotherapy and Oncology, 123(2), pp.294-298.	Included
3	Proton Beam Therapy Model Policy, ASTRO Model Policies, American Society for Radiation Oncology Available from ASTRO website: https://www.astro.org/Daily-Practice/Reimbursement/Model-Policies	Not included. This is policy not a study and is therefore not eligible for inclusion in this evidence review.

12 References

Bradley JA. Dagan R. Ho MW. Rutenberg M. Morris CG. Li Z. Mendenhall NP. 2016. Initial report of a prospective dosimetric and clinical feasibility trial demonstrates the potential of protons to increase the therapeutic ratio in breast cancer compared with photons. *International Journal of Radiation Oncology Biology Physics* 95(1): 411-421.

Bush DA. Do S. Lum S. Garberoglio C. Mirshahidi H. Patyal B. Grove R. Slater JD. 2014. Partial breast radiation therapy with proton beam: 5-year results with cosmetic outcomes. *International Journal of Radiation Oncology Biology Physics* 90(3): 501-505.

CADTH. 2017. Proton beam therapy for the treatment of cancer in children and adults. Health Technology Assessment 145. Available from https://www.cadth.ca/sites/default/files/pdf/HT0017_PBT_Report.pdf (Accessed June 2018).

Cancer Research UK (CRUK). 2019a. Breast cancer statistics. Available from https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer#heading-Zero (Accessed August 2019).

Cancer Research UK (CRUK). 2019a. Breast cancer. Available from https://www.cancerresearchuk.org/about-cancer/breast-cancer (Accessed August 2019).

Chang JH. Lee NK. Kim JY. Kim YJ. Moon SH. Kim TH. Kim JY. Kim DY. Cho KH. Shin KH. 2013. Phase II trial of proton beam accelerated partial breast irradiation in breast cancer. *Radiotherapy and Oncology* 108: 209-214.

Chowdhary M. Lee A. Gao S. Wang D. Barry PN. Diaz R. Bagadiya NR. Park HS. Yu JB. Wilson LD. Moran MS. Higgins SA. Knowlton CA. Patel KR. 2019. Is proton therapy a “pro” for breast cancer? A comparison of proton vs. non-proton radiotherapy using the national cancer database. *Frontiers in Oncology* 8 (January): Article 678.

Cuaron JJ. Chon B. Tsai H. Goenka A. DeBlois D. Ho A. Powell S. Hug E. Cahlon O. 2015. Early toxicity in patients treated with postoperative proton therapy for locally advanced breast cancer. *International Journal of Radiation Oncology Biology Physics* 92(2): 284-291.

DeCesaris CM. Rice SR. Bentzen SM. Jatczak J. Mishra MV. Nichols EM. 2019. Quantification of acute skin toxicities in patients with breast cancer undergoing adjuvant proton versus photon radiation therapy: a single institutional experience. *International Journal of Radiation Oncology Biology Physics* 104(5): 1084-1090.

Liang X. Bradley JA. Zheng D. Rutenberg M. Yeung D. Mendenhall N. Li Z. 2018. Prognostic factors of radiation dermatitis following passive-scattering proton therapy for breast cancer. *Radiation Oncology* 13: 72.

Luo L. Cuaron J. Braunstein L. Gillespie E. Kahn A. McCormick B. Mah D. Chon B. Tsai H. Powell S. Cahlon O. 2019. Early outcomes of breast cancer patients treated with post-mastectomy uniform scanning proton therapy. *Radiotherapy and Oncology* 132: 250-256.

MacDonald SM. Patel SA. Hickey S. Specht M. Isakoff SJ. Gadd M. Smith BL. Yeap BY. Adams J. DeLaney TF. Kooy H. Lu HM. Taghian AG. 2013. Proton therapy for breast cancer after mastectomy: early outcomes of a prospective clinical trial. *International Journal of Radiation Oncology Biology Physics* 86(3): 484-490.

Ovalle V. Strom EA. Shaitelman S. Hoffman K. Amos R. Perkins G. Tereffe W. Smith BD. Stauder M. Woodward W. 2018. Proton partial breast irradiation: detailed description of acute clinic-radiologic effects. *Cancers* 10, 111.

Smith NL. Jethwa KR. Viehman JK. Harmsen WS. Gonuguntla K. Elswick SM. Grauberger JN. Amundson AC. Whitaker TJ. Remmes NB. Harless CA. Boughey JC. Nguyen MDT. Park SS. Corbin KS. Mutter RW. 2019. Post-mastectomy intensity modulated proton therapy after immediate breast reconstruction: initial report of reconstruction outcomes and predictors of complications. *Radiotherapy and Oncology* 140: 76-83.

Teichman SL. Do S. Lum S. Teichman TS. Preston W. Cochran SE. Garberoglio CA. Grove R. Davis CA. Slater JD. Bush DA. 2018. Improved long-term patient-reported health and well-being outcomes of early-stage breast cancer treated with partial breast proton therapy. *Cancer Medicine* 7: 6064-6076.

Verma V. Shah C. Mehta MP. 2016. Clinical outcomes and toxicity of proton radiotherapy for breast cancer. *Clinical Breast Cancer* 16(3): 145-54.

Verma V. Iftekaruddin Z. Badar N. Hartsell W. Chang JHC. Gondi V. Pankuch M. Gao M. Schmidt S. Kaplan D. McGee L. 2017. Proton beam radiotherapy as part of comprehensive regional nodal irradiation for locally advanced breast cancer. *Radiotherapy and Oncology* 123: 294-298.